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Vol. 21 MARCH, 1947 No. 3

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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Vol. 21, No. 3, March, 1947. Surgery is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its possessions, Pan-American Countries, $10.00 a year; Canada and Foreign, $11.00. Entered as Second-Class Matter January 20, 1937, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in U. S. A.

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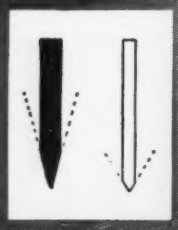

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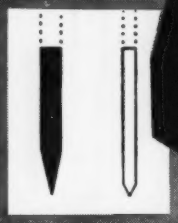

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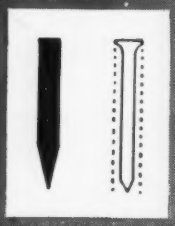

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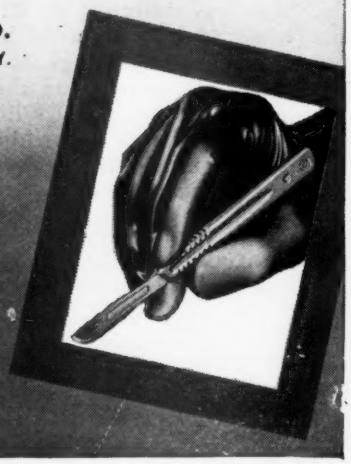

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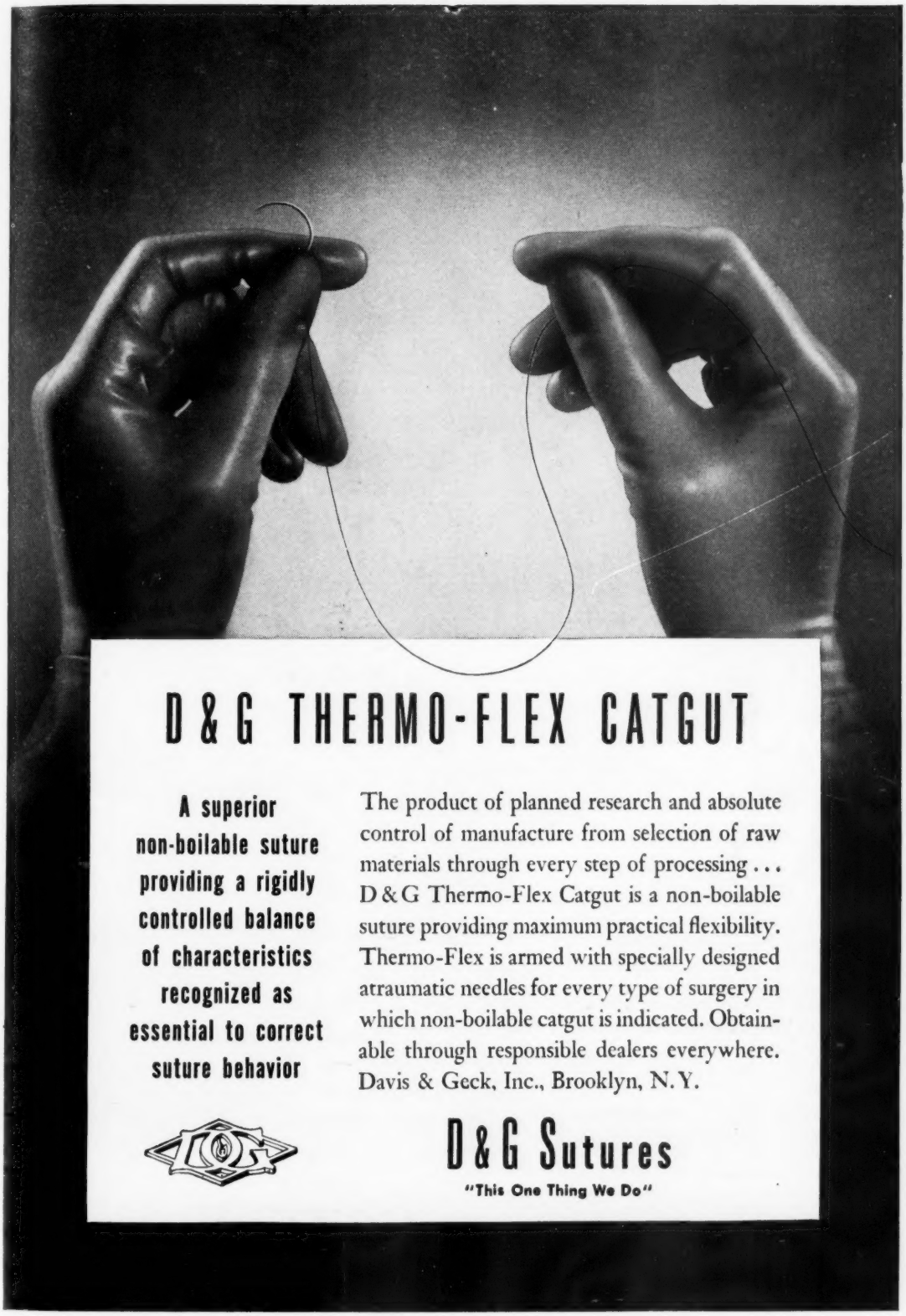
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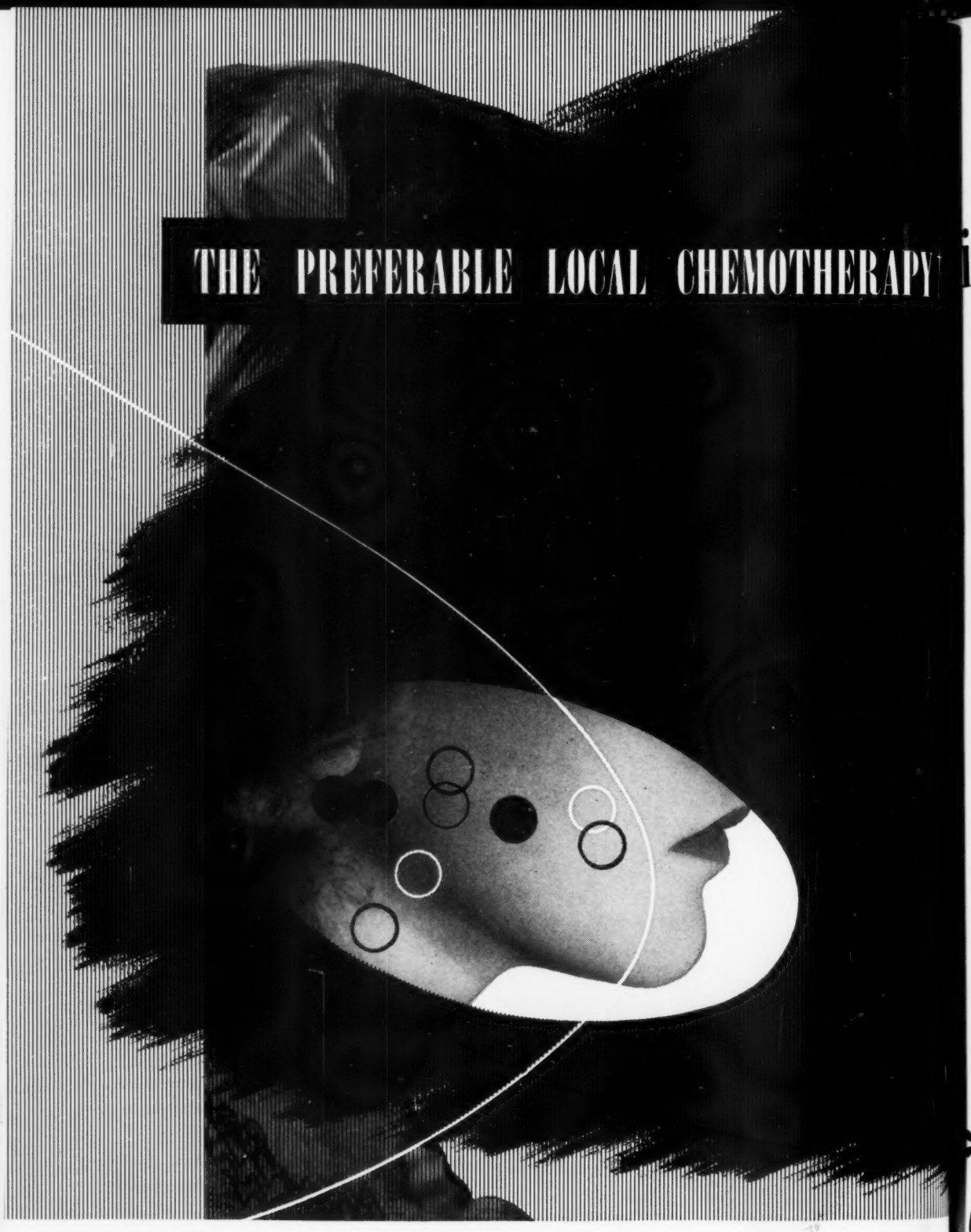

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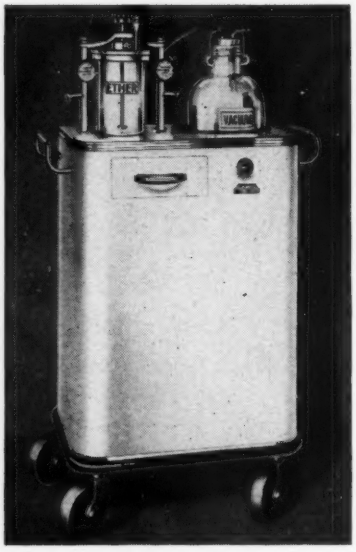

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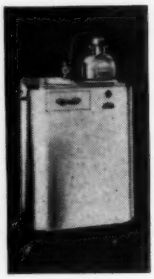

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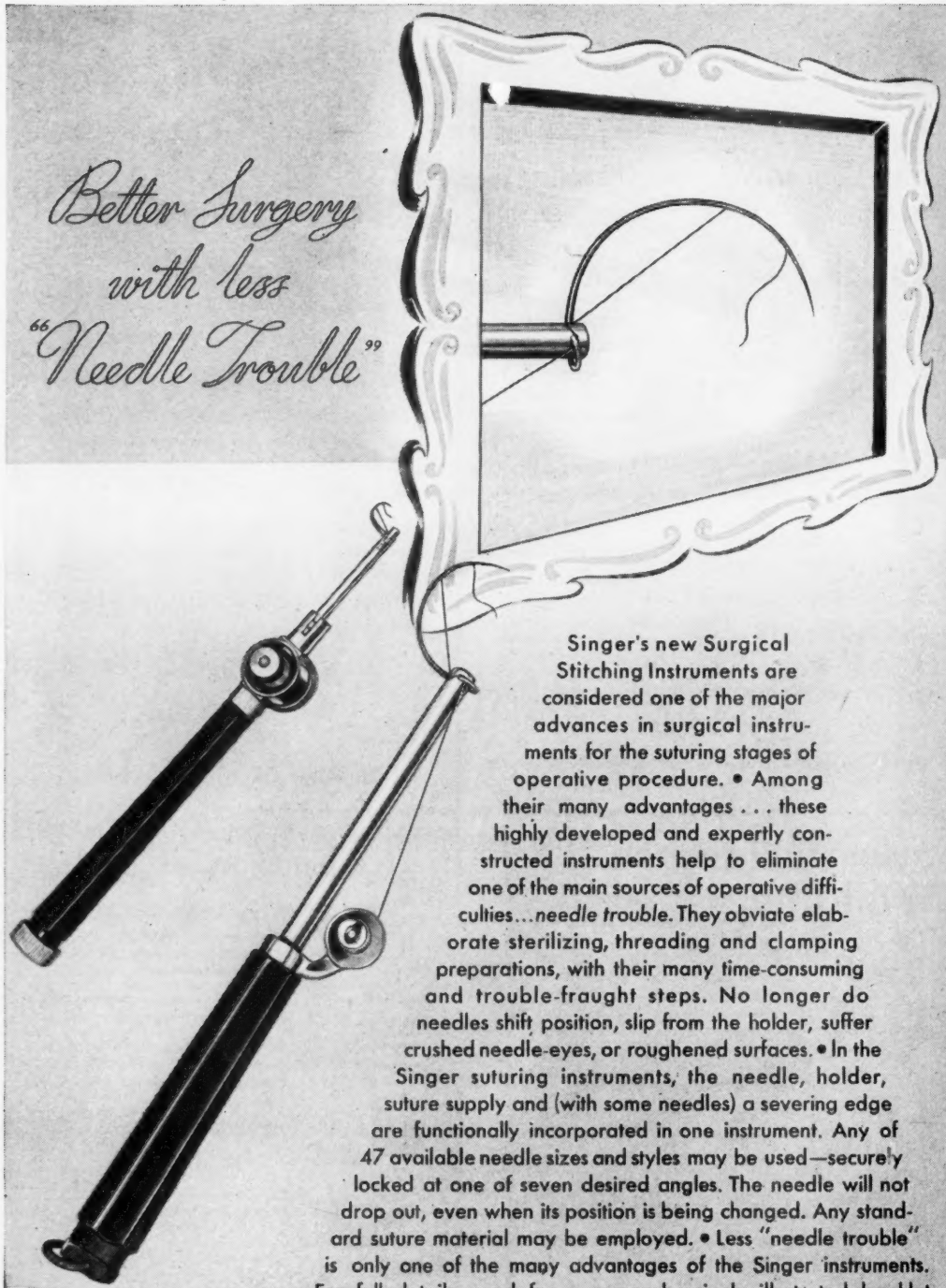

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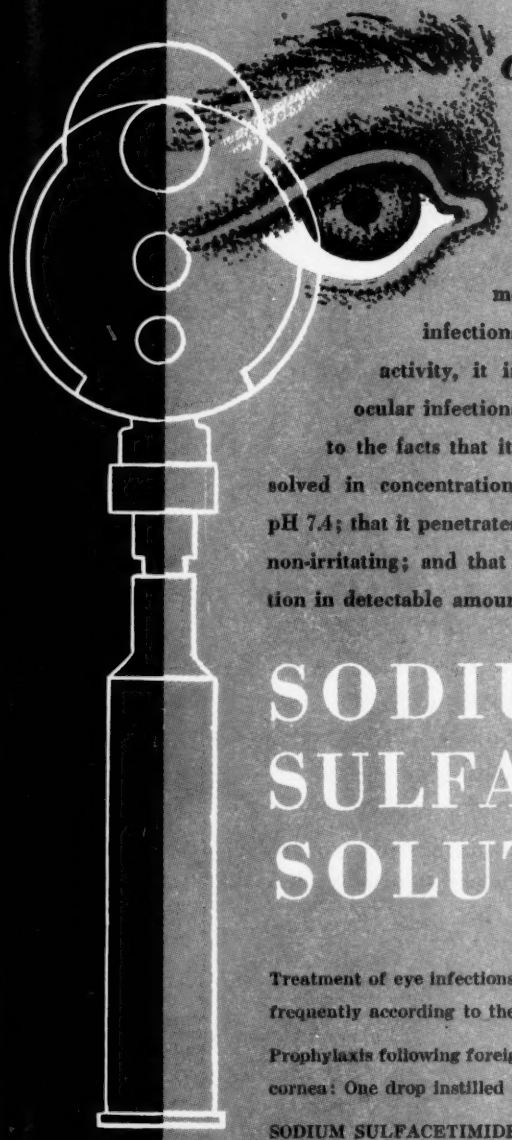

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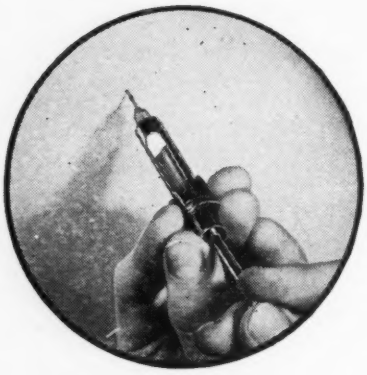

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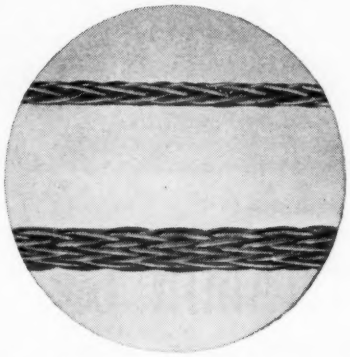

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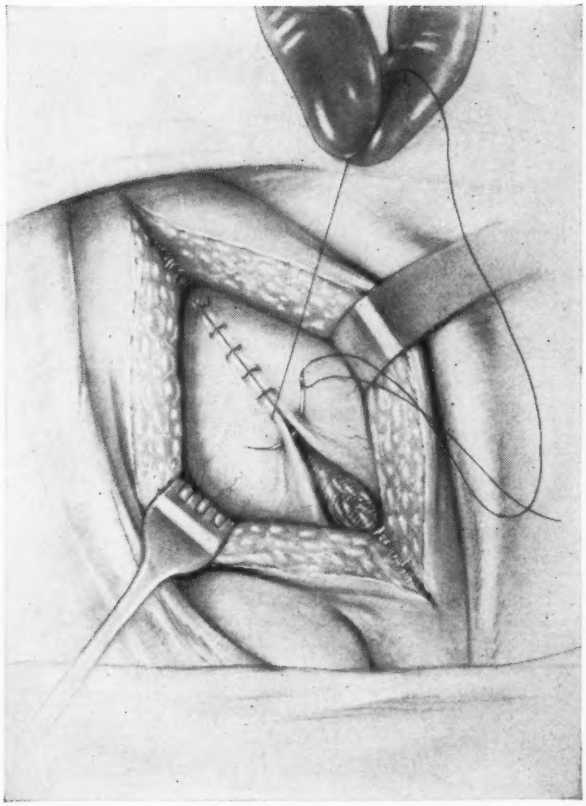

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IN THIS paper we present a series of thirty-four consecutive cases of open anastomosis in various parts of the large bowel. There was no mortality directly attributable to surgery. There were two deaths in the thirty-four cases. The first occurred in a 62-year-old woman patient on the seventeenth postoperative day, following a segmental resection with primary anastomosis for cancer of the sigmoid. The patient was to have been discharged from the hospital the following day, but died suddenly of a pulmonary embolism. The second occurred in a 58-year-old woman on the sixth postoperative day following a primary resection of the sigmoid for cancer. This patient died of a coronary thrombosis. These anastomoses were performed over a period of twenty-seven months (September, 1943, to January, 1946). In none was a complementary cecostomy used; all patients received the routine preparations outlined in this paper. Seven of the patients had obstruction or partial obstruction on entrance to the hospital, but were relieved of their obstruction (as outlined below), so that a primary anastomosis could be performed at a later date with safety. No patient developed a fecal fistula and no patient developed obstruction after operation.

The changing history of bowel resections is fascinating, if only to note how the recent application of modern biochemical and physiologic principles has helped us approach more ideal surgery with less trepidation than in the past.

The earliest bowel resections were completed with primary anastomosis. Most of these attempts, however, were discouraging.

The first successful resection with primary anastomosis was performed in 1833 by Reybard on a 28-year-old man who had carcinoma of the sigmoid. In 1843 Thiersch resected an acutely obstructed colon. By 1880 ten resections had been recorded, three of which were successful. In 1881 Kocher reported a successful resection with end-to-end anastomosis. By 1881 Billroth had reported

Received for publication, March 29, 1946.

seventeen cases with ten deaths, a mortality of about 60 per cent. By 1889 his clinic had reported fifty-seven cases with nineteen deaths, a mortality of 37 per cent.

More than 60 per cent of the operative deaths were due to peritonitis. The era of resection with primary end-to-end anastomosis was fast coming to a temporary interruption. In its place surgeons were encouraged to use the multiple stage operations of which the so-called Mikulicz operation is best known. The only well-supported claim for its popularity was found in the reduced mortality over that of the single stage resection with primary anastomosis.

In reporting sixteen cases with two deaths, a mortality of 12.5 per cent, Mikulicz lowered considerably the best previously reported mortality, namely, 37 per cent.[22] However, this procedure never attained universal acceptance because of certain undesirable features: From the standpoint of the patient—the uncomfortable flow of feces over an excoriated skin, the multiplicity of operations, the time consumed, and the expense of several hospital stays. From the standpoint of the surgeon—the limitations on the amount of mesentery which may be excised without impairing the blood supply (such impairment leading to necrosis, leakage into the peritoneal cavity, and death), the danger of implantation of cancer cells in the abdominal wound because not enough of the carcinomatous mesentery can be excised safely, and the impossibility of exteriorizing bowel with a short, fat mesentery.

In spite of the progressive ascendence of the use of the exteriorization procedure, there were always a few intrepid, visionary surgeons who attempted and hoped to achieve successfully the ideal primary anastomosis.[7, 13, 14, 17, 19, 26] And if they failed, it was not always because their technique was inadequate or contaminating. They failed many times because they did not recognize certain fundamental principles of colon physiology and pathology.

Practically every cancer of the colon, especially the left colon, is partially obstructive. Multiple enemas and continuous intestinal decompression by suction had not yet come into vogue. Had the surgeon a better knowledge of these valuable adjuncts (so that the colon could be emptied adequately before surgery, permitting the distended, hypertrophied, and edematous intestinal wall to regain its normal tone and size), primary anastomosis would have been the procedure of choice in resectable, nonobstructive carcinoma of the colon. No technique, open or closed, will give a high rate of successful primary anastomosis if the sutures have to be taken through soft, boggy tissues and in the presence of infection. Yet that is what the pioneer surgeons attempted. No wonder they had a high mortality. More wonder their success, as small as it was. With this ideal of primary anastomosis in mind it was no surprise that surgeons attempted to devise instruments and methods[19, 24] which would theoretically prevent contamination of the suture line and peritoneal cavity. In 1891 Halsted[13] attempted to develop a relatively aseptic method. He emphasized the fact that the submucous layer of the gut wall was the true layer of strength; hence, all that was necessary was to perforate the submucous layer without penetrating the mucosa. This was, and is, a theoretical not a practical solution. Moreover, it was due more to a late leak at the suture

line and less to a contamination at operation which led to the terrible incidence of peritonitis. This fact seems to have escaped early workers.

About this time other surgeons attempted closed anastomosis by clamping the ends of the two limbs of bowel and performing an anastomosis over the clamps. The diaphragm between the two limbs was then broken with the fingers after the clamps were removed. In 1908 Parker and Kerr[26] used a so-called basting stitch to close the ends of the bowel, made their closed anastomosis, and then removed the basting stitch. Again the diaphragm had to be broken down by finger manipulation. Both Horsley and Stone have had obstructions with this method.[4] Other men have been enthusiastic over closed methods of anastomosis (Schoemaker,[31, 32] Halsted,[14] Fraser and Dott,[10] Furniss[11]). However, obstructions have been reported with methods of Halsted and Fraser and Dott due to projection of tissue into the lumen at the line of anastomosis.[4] Senn pointed out that "If . . . more than a few lines of the margin of the bowel is inverted between the two rows of sutures, there is great danger of causing primary traumatic stenosis of the projecting circular ring in the lumen of the bowel."[7]

In recent years Rankin,[29] Gibbon and Hodge,[12] Owings and Stone,[25] Stone and McLanahan,[35] Wangensteen,[37] and others have been ardent exponents of the *closed* method. Yet Charles W. Mayo was able to report a mortality of 8.4 per cent with eighty-three cases of carcinoma of the right colon, counting deaths from all causes regardless of the time spent in the hospital.[18] Open, one-stage anastomosis was used in these cases. In 1931 Cheever[6] reported a series of interesting cases, using an *open* method of anastomosis. He achieved the low mortality of 8.5 per cent when a complementary cecostomy or colostomy was used. Without a complementary vent his mortality went up to 24 per cent. However, with the use of continuous suction such complementary vents are not only unnecessary, but are in fact a burden because of potentially infected wounds, further operations, etc.

Some twelve years later Whipple was able to point out "that with the proximal bowel decompressed (by use of Miller-Abbott tube and suction), the hazard of spillage and contamination is eliminated and the anastomosis by the open method, with careful protection of the wound and remaining peritoneum and accurate suture technique, is as safe as the so-called aseptic methods, and more certain of giving an adequate stoma and avoiding subsequent leakage."[38]

It can hardly be denied that it is much better to work with freshly cut edges (not crushed ends) under direct visual inspection and see each stitch accurately placed than to suture crushed edges with sutures that cannot be visualized completely. We have no special prejudice against mechanical gadgets as such, but where these become a possible blind for fundamental principles, we advise caution.

Preoperative Preparation of the Colon.—The principles of preoperative care involve thorough cleansing of the bowel; fortification of the liver with respect to glycogen storage; correction of dehydration, anemia, protein, and vitamin deficiencies; general restorative measures; sulfonamide prophylaxis; the use

of suction when properly indicated; *fluoroscopic examination in all bowel cases to eliminate any possibility of the presence of retained barium.*

On admission the patient with carcinoma of the colon falls into one of two classes: (1) Obstructive or partially obstructive; (2) nonobstructive. The treatment of these types varies accordingly.

OBSTRUCTIVE CASES

The extent of the pathology in the colon in the obstructive phase determines operability. During the final stages of an obstruction due to carcinoma of the colon, when a partial obstruction becomes complete, the proximal colon becomes distended and there is encroachment upon the blood supply, with devitalization of the mucosa and consequent ulceration. The highly virulent bacteria seep through the soggy, edematous wall, so that the patient becomes toxic and has a low-grade fever. If the patient gets no relief, perforation may occur. A patient with such an obstruction presents all the physiologic and anatomic problems of an individual with a margin of safety so narrow that he must have the benefits of well-planned pre- and postoperative attention if he is to survive. The patient has usually had a restricted diet and is vomiting, dehydrated, and anemic.

The management of the obstructive phase requires careful observation and the use of ingenious nonoperative methods for relieving the obstruction. The patient is typed and cross-matched and receives immediate intravenous fluids. A Levine duodenal tube is inserted intranasally and continuous suction started immediately. A cleansing enema is given, and one hour later the patient receives one ounce of mineral oil by mouth. When the oil is given, the suction is stopped for twenty minutes. The enemas and mineral oil are administered on alternate hours until the oil comes through in the enema washings or until the patient is passing gas and feces freely by rectum.

The purpose of this regime is to convert a complete or partial obstruction into a nonobstructive lesion. When a carcinomatous lesion produces obstruction, it is mainly the secondary features of the carcinoma (with all that this implies, such as inflammation, impaired circulation, and edema in and about the lesion) which obstruct the lumen. Not infrequently a bit of inspissated feces or barium (administered either by mouth or by rectum) plugs the narrow lumen and, together with the increasing inflammation and edema, produces a complete obstruction.

Feces are usually liquid in the right colon and more dehydrated in the left; hence, the lower-lying lesions are the ones which obstruct early.[30] If one is able to dislodge the feces or barium by large enemas from below and relieve the forward pressure by suction from above, then there is a better chance for the secondary edema to subside. The lumen in the region of the lesion will enlarge and gas and feces will pass.

Once such a patient shows signs of increased peristaltic sounds and passage of gas and feces and oil from below, suction is stopped and the patient is put on a course of succinylsulfathiazole. A liquid, nonresidue diet is given for a few days and is then changed to a high protein, high carbohydrate, low

fat, low residue diet. A soapsuds enema is given twice daily. The day before surgery an enema is given every two hours or until the returns are clear. The colon must be thoroughly cleansed with repeated enemas and all residual barium washed out (as shown by preoperative fluoroscopy). Food is stopped twenty-four hours before surgery, but the succinylsulfathiazole is continued.

Any attempt to do a successful end-to-end anastomosis must assume that the patient has been brought back to near physiologic normal, both locally and systemically. The colon must be empty and it must possess normal tone and normal healing powers.

NONOBSTRUCTIVE CASES

Nonobstructive cases offer no serious problem of preoperative preparation. The patient is given a purge, usually one ounce of magnesium sulfate; large, cleansing enemas twice daily; succinylsulfathiazole is administered by mouth, together with a high protein, high carbohydrate, low residue diet. The plasma, hemoglobin, and vitamin levels are checked and brought up to par. At the end of about one week the patient is usually ready for surgery.

Preoperative Preparation.—The entire late history of the problem of primary anastomosis revolves intimately about the newer concepts of adequate pre- and postoperative management.

Sulfonamide Prophylaxis.—One of the causes for poor end results in large bowel surgery, especially in primary anastomosis, has been peritonitis due to late leaks through the suture line and bacterial contamination of the peritoneal cavity. Ever since Moore and Miller (in 1942) synthesized and Poth[28] demonstrated the intestinal antiseptic action of succinylsulfathiazole, there has been strong hope that primary anastomosis of the bowel would become a much safer procedure. Succinylsulfathiazole approaches the ideal antiseptic because it is poorly absorbed from the alimentary canal and has strong bacteriostatic properties. Even though it does not sterilize the feces, it helps bring about a marked reduction in the *Escherichia coli* and anaerobic bacilli stool count. After one week of administration, according to Poth, the *Esch. coli* count drops from an average of 10 million to less than 1,000 organisms per gram of wet stool. Since succinylsulfathiazole is so poorly absorbed from the intestinal tract (blood levels vary between 1 and 2.5 mg. per cent), it has a low antibacterial action in the peritoneal fluids.

Succinylsulfathiazole has additional virtues perhaps not considered in its original use. It so alters the bacterial flora that the consistency of the stool after one to seven days of therapy becomes "semi-fluid, small in bulk, somewhat gelatinous in appearance, and relatively odorless." The bowel becomes free of gross fecal material and gas. In addition, succinylsulfathiazole is relatively nontoxic.

The colon bacilli reappear rapidly in the feces on withdrawal of succinylsulfathiazole. Hence, the oral administration of the drug is begun as soon as possible postoperatively. This in itself produces little or no vomiting and the readministration of the drug may start within the first twenty-four hours postoperatively. The period required for achieving maximum reduction in

TABLE I. ORDERS FOR NONOBSTRUCTIVE BOWEL CASES

PREOPERATIVE PROCEDURE

Work-up
1. Complete blood count
2. Urinalysis
3. Wassermann and Kahn
4. Blood cevitamic acid
5. X-rays (as directed by surgeon)
6. Type patient and obtain compatible donors
7. Stool to laboratory
8. Weigh patient
9. Special tests as indicated:
   (a) Total blood protein
   (b) A/G ratio

Medication
1. Succinylsulfathiazole
   (a) 0.25 Gm. per kilogram body weight per 24 hours
   (b) 0.25 Gm. given as one dose Stat., then 1/6 of that amount given every 4 hours thereafter for 5 days before surgery
   (c) In instances where the patient cannot tolerate such a large initial dose, the drug can be administered more gradually, i.e., 3 Gm. every 4 hours for 7 to 14 days preoperatively
2. Cevitamic acid, 1,000 mg. in divided doses
3. Hi-vitamin capsules, 1 t.i.d.
4. Fluids, 3,000 c.c. daily (q.v.)
5. Blood transfusion, plasma, or amino acids
6. Mineral oil, 1 oz. q. nightly
7. Urotropin, gr. 7½, t.i.d. for 5 days
   Sodium acid phosphate, gr. 10, before surgery
8. Antiseptic mouthwashes
9. Night medication
10. Morphine sulfate, gr. 1/6
    Scopolamine, gr. 1/150, 1 hour before surgery

Management
1. Hi-carbohydrate diet (nonresidue)
2. Dexin sweetened fluids and fruit juices between meals
3. Normal saline enemas, 2 to 4 times daily
   (a) Saline solution enema once or twice daily for 3 days before surgery and every 2 hours on the day before surgery until returns are clear
   (b) If the lesion can be visualized through a proctoscope the bowel may be cleansed further by irrigating through a catheter inserted beyond the lesion

POSTOPERATIVE PROCEDURE

Work-up
1. Record fluid intake and output
2. Complete blood count } as ordered
3. Urinalysis }

Medication
1. Morphine sulfate, gr. 1/6, for pain or restlessness
2. Antiseptic mouthwashes
3. Fluids, 3,000 c.c. per 24 hours
4. Sodium sulfadiazine in distilled water, 5 Gm. daily for 2 or 3 days postoperatively
5. Penicillin (as ordered by surgeon)

Management
1. Nothing by mouth until ordered.
2. Catheterization q. 12 to 15 hours or for distress (instill 5% argyrol after catheterization)
3. Blood transfusion as indicated
4. Oxygen (if necessary)

colon bacteria is from five to seven days. The drop for *Clostridium welchi* and *Streptococcus fecalis* rather closely parallels the drop in the number of colon bacilli except that it takes a little longer—six to eight days. We have been using the following dosage of the drug: 0.25 Gm. per kilogram body

weight per twenty-four hours given as one large dose stat., and one-sixth of the original dose given every four hours. The same dose has been used postoperatively.

We must realize, however, that sulfonamide prophylaxis and therapy must not alter good judgment in the selection of cases, nor make for poor surgical technique, nor fail to take cognizance of other important pre- and postoperative measures.

Protein and Hemoglobin Levels.—Any patient who has a well-marked anemia should be regarded as a questionable risk for surgery. We are thoroughly familiar with the diminished oxygen-carrying power of hemochromic and cytopenic anemias, but we are probably not as conscious of hypoproteinemias and tissue protein deficiencies as their importance would warrant. The term *protein deficiency* is more appropriate than *hypoproteinemia* because the latter is a description of the circulating proteins which merely mirror the total protein depots of the body. When there is sufficient depletion of tissue proteins, then the circulating proteins manifest themselves as a hypoproteinemia (the ratio of tissue to circulating proteins is considered to be 30:1).[21]

The hypoproteinemic patient may develop generalized edema, including edema of the viscera, brain, and gastrointestinal tract. Edema of the colon may lead to subsequent obstruction of the new stoma (in cases of primary anastomosis) with nausea and vomiting and possible rupture of the suture line. Edema of the kidney may lead to a nephrotic syndrome with oliguria or anuria. Furthermore, hypoproteinemia produces a deficient tissue collagenic reaction with impaired wound healing. Of all major surgery, carcinoma of the colon, bowel obstruction, and generalized peritonitis produce the largest decrease in plasma proteins.[21]

These findings suggest that a very determined effort should be made to correct protein deficiencies in all patients who undergo major surgery, especially patients with carcinoma of the bowel. Correct use of plasma, whole blood (which produces a greater rise in protein levels than does plasma), amino acids, dextrose, and saline solutions must depend on frequent observations of the patient's total plasma protein levels, hematocrit readings, and hemoglobin estimations. We should like to stress the point that in patients with protein deficiencies, transfusions of less than 2,000 c.c. rarely bring the total plasma protein levels up to minimal requirements. The slow response in plasma protein levels implies extensive tissue protein depletion which must be satisfied before plasma protein levels offer an accurate index.

Hence, it has been our policy for some time to take total protein and albumin-globulin ratio levels on all patients undergoing major surgery, especially those who may have had long-standing dietary imbalances with reference to protein and vitamin intake. These patients have starved themselves either voluntarily because of a sitophobia or because the prescribed diet to relieve the gastrointestinal distress had been insufficient. The patient with a low total protein or a reversed albumin-globulin ratio is a poor risk from the standpoint of postoperative management.

Vitamin Therapy.—Wound healing and the reparative processes which accompany intestinal anastomosis are a function of the tissue depots of the body as reflected by the plasma protein of the blood; however, they also depend on the efficient levels of other factors. It is of little avail to saturate a surgical patient with proteins if the lack of these other factors is not adjusted. It has been demonstrated repeatedly that low vitamin C levels manifest themselves histologically by the lack of collagen which is a basic substance of tissue repair. With this defect in collagen production the whole architecture of the healing wound is disturbed.[15] It has been our practice to determine vitamin C levels as soon as the patient is admitted. When subnormal levels are found, we begin large doses of vitamin C intravenously: 1,000 mg. of vitamin C are given daily, preferably in divided doses in the preoperative intravenous glucose or salt solutions. These are supplied by the slow drop method. This type of management is predicated on the fact that there is a very low renal threshold for vitamin C. Its rapid elimination from the blood may be minimized and the effective rate of tissue absorption increased by prolonging the period of administration. The ability of the tissues to absorb and store vitamin C is limited as to rate, and tissue saturation even with very large doses cannot be attained before five to seven days. However, the most acute need for collagen efficiency occurs when the sutures which have been inserted begin to cut through and lose their supportive strength. This period is somewhere between the third and seventh postoperative days. Thus, in a patient with a very low vitamin C level, tissue saturation could be attained at the time of greatest need if the patient were placed on a high vitamin C regime immediately on the decision to operate or upon admission to the hospital.

Prothrombin levels are checked preoperatively and adjusted accordingly either with synthetic vitamin K substances or with liberal fresh whole blood transfusions. We use routinely 5 to 10 mg. of vitamin K daily in the preoperative intravenous fluids.

Vitamin B complex deficiencies manifest themselves in vicious cycles in which absorption and utilization from the gastrointestinal tract become progressively impaired. A surgical patient has an increased need for the vitamin B complex due to the parenteral use of glucose and saline solutions. The oxidation of carbohydrates utilizes the B coenzyme factors, and the increased diuresis carries with it water-soluble B vitamins. Impaired preoperative absorption and postoperative dietary restrictions lead further to depletion of the B complex stores. We attempt to re-establish and maintain tissue saturation of the B complex by daily administration in the pre- and postoperative intravenous fluids.

Postoperative Management.—The gastrointestinal tract is kept at rest as long as possible postoperatively. The patient is usually given a transfusion on the first or second postoperative day. The plasma and vitamin levels are maintained and the fluid balance controlled. The Levine tube is kept in place during surgery and postoperatively until the patient begins to pass gas and feces freely per rectum. Before the patient is removed from the operating table, the sphincter control of the anus is temporarily paralyzed by dilatation.

This protects the patient if the nurse neglects to insert an indwelling rectal tube or if the tube becomes plugged and is not cleansed or if it comes out and is not re-inserted immediately.

We use the Levine tube in preference to the Miller-Abbott tube because not only does it work well in the majority of instances, but it is easier to insert and it obviates postoperative gastric distention; whereas the Miller-Abbott tube, if very far down in the small intestine, may deflate the small intestine, but have no effect on the stomach.

The Technique of Open Anastomosis.—The use of clamps is decried not so much for the increased difficulty in application as for the difficulty in suturing around such clamps and for the difficulty in removing them after the anastomosis is completed. Furthermore, nearly all such methods of anastomosis include a running stitch around the bowel which is dangerous for reasons given elsewhere in this paper.

The mesentery, which is to be resected, must be freed up so that it has no structures attached to it, for example, the right or left ureter or the retroperitoneal portion of the duodenum. The mesentery is divided and ligated before resection. The blood vessel aborization is examined carefully and enough blood vessels are left for adequate vascularization of the ends to be anastomosed. In this respect the classical works of Monks[23] and Drummond[9] are apropos. In more recent years Steward and Rankin[34] and others have emphasized the importance of considering the blood vessel distribution in each resection and also the importance of not underestimating the significance of the appendices epiploicae in the blood supply to the colon. Even with this in mind there is no substitute for accurate suturing of the gut wall (especially the submucous layer which is the only layer of real strength holding the suture). In order to achieve this purpose, it may be necessary occasionally to remove carefully the appendices epiploicae for a short distance from the cut ends of the bowel.

Where an end-to-end anastomosis is proposed and the diameters of the ends are too greatly dissimilar, the diameter of the smaller end may be increased and made equal to the large one by cutting its antimesenteric side and placing it on a slight bias.

In a typical end-to-end anastomosis, after the abdominal exploration is completed (metastases to the liver, aortic glands, and mesentery noted), the mesentery is freed from the underlying structures and lifted up. As emphasized by Lockhart-Mummery,[16] rubber-covered clamps are applied to the bowel in an angular fashion a suitable distance (usually about four inches) on each side of the lesion to be resected. The mesentery is doubly clamped, divided, and suture-ligated. The bowel is double clamped with Ochsner forceps at a suitable distance distal and proximal to the lesion, but within the curved rubber-covered clamps, and the bowel is held up with two Babcock forceps. The lesion and the adjacent colon are removed with attached mesentery in a triangular fashion. In the pelvic colon the distal end need not be clamped because it should be free from any fecal content.

The rubber-covered clamps are brought side-to-side, mesenteric edge to mesenteric edge. One suture is now inserted at the mesenteric attachments of the cut ends and another at the antimesenteric ends. Low down in the

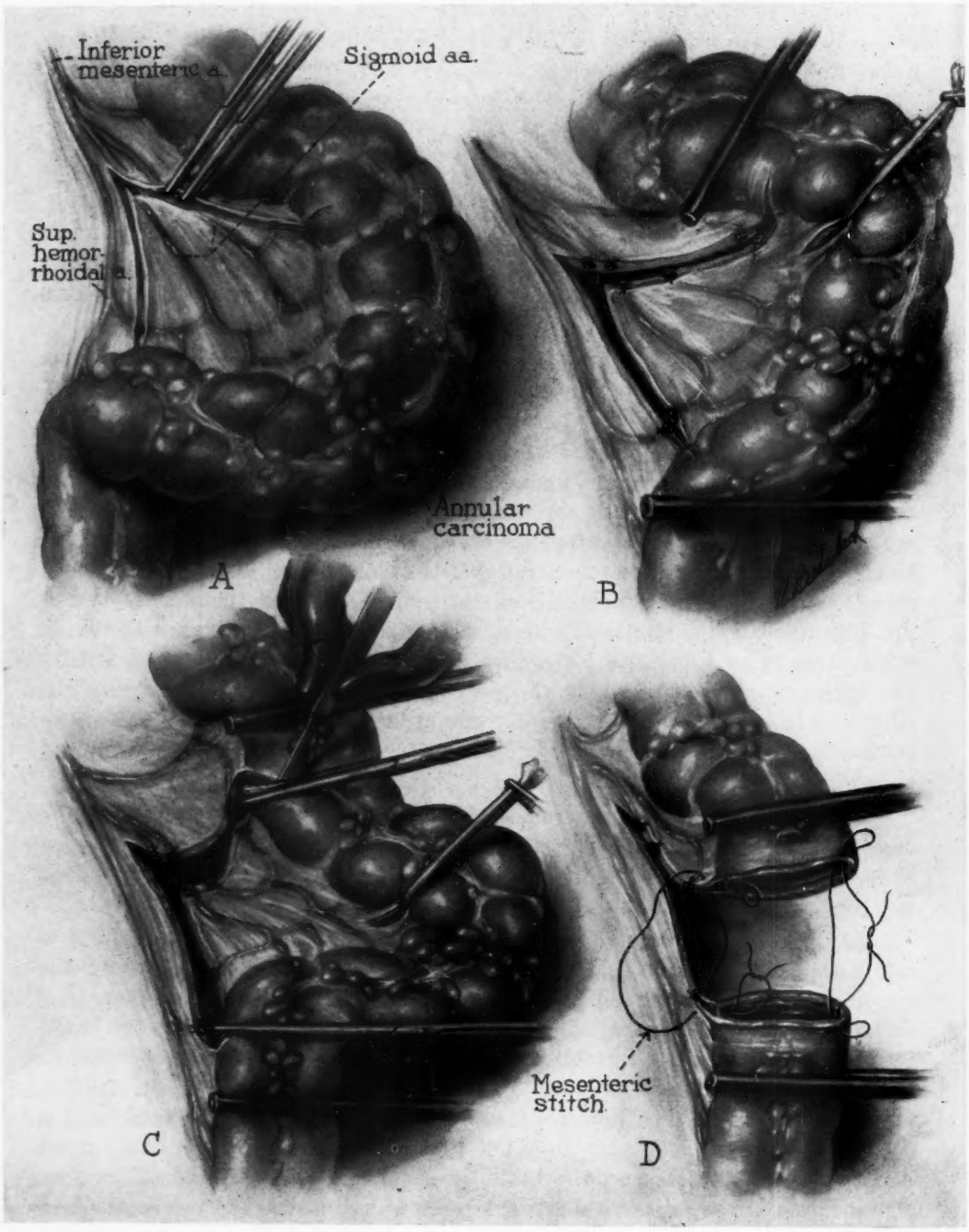

Fig. 1, *A-D*.—The isolation of the lesion and division of the mesentery are shown; the location of the clamps should be noted.

pelvis it may be easier to apply the first sutures at either end of the transverse diameter of the bowel. The suture at the mesenteric side is the so-called Maunsell suture.[17] These sutures are illustrated in Fig. 1, *D*. The suture goes through all the coats of the bowel and acts as a brad. The knot is tied on the mucosa, the ends are left long, and a forceps is applied to the long ends.

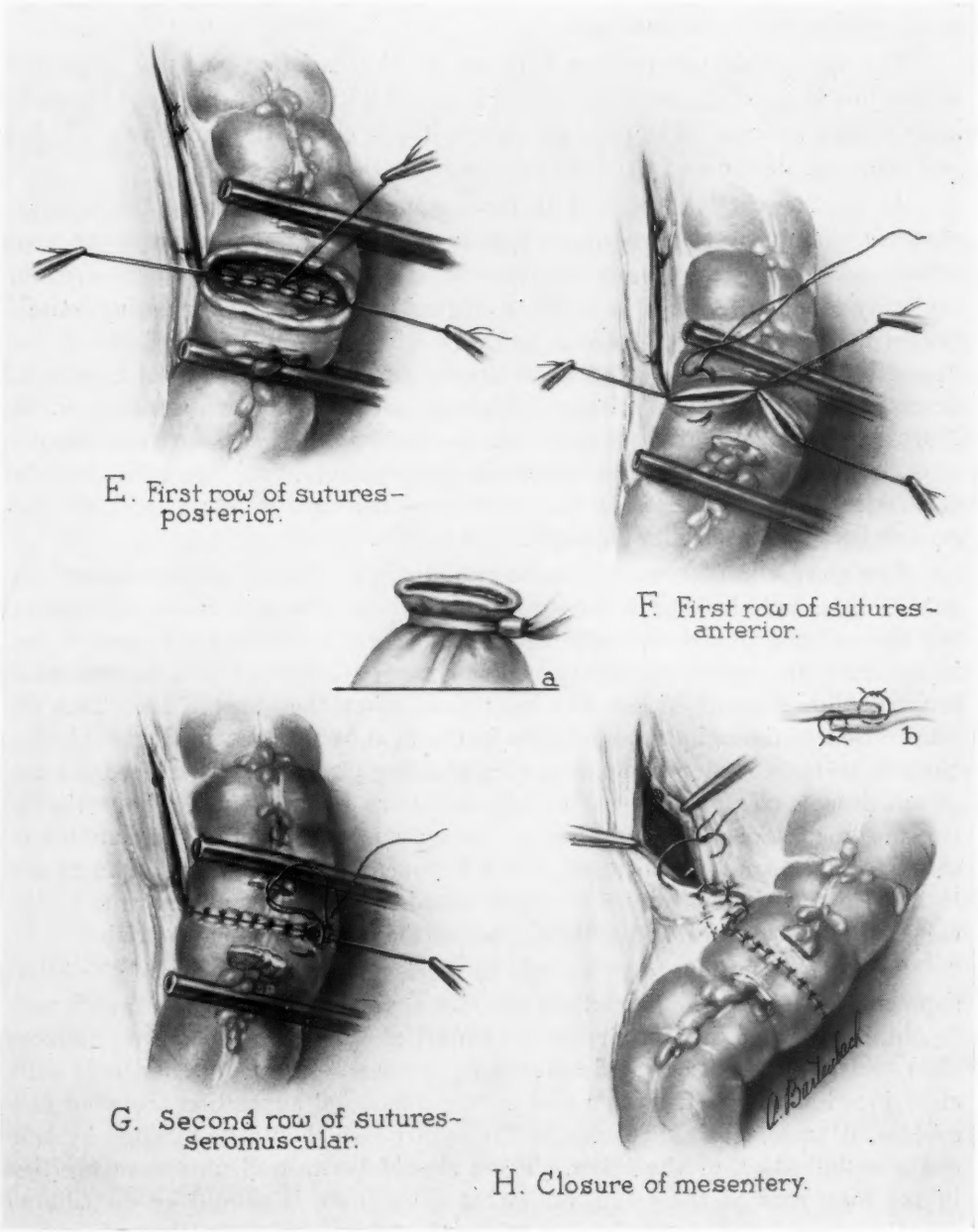
E. First row of sutures - posterior.
F. First row of sutures - anterior.
a
b
G. Second row of sutures - seromuscular.
H. Closure of mesentery.

Fig. 1, *E-H*.—The careful spacing of the sutures is shown. The fresh nontraumatized edges of the resected bowel are clearly visualized. (*a*) A tape may be applied if it is difficult to adjust a rubber-covered clamp.

The second suture at the antimesenteric side is a Connell[8] suture through all the coats of the cut ends of the bowel. It is also knotted on the mucosa, the ends left long, and a forceps applied to the long ends.

These sutures are most important. They secure the complete peritoneal covering of the mesenteric attachment of both segments of the gut and also act as guide ropes to help maintain the proper relative position and accurate co-adaptation of the two cut ends.

The two guide sutures are held up by the assistant and the posterior suture line is bisected and then further bisected with carefully spaced through-and-through sutures. The anterior suture line is closed the same way. A second seromuscular row of Lembert sutures is applied.

At all times it is important to have a smooth adaptation of the mucosal surfaces. A mucosal arrangement that creates a flute-valve effect is the most efficacious. Leaks are prone to occur where the mucosal surfaces are not smoothly opposed. This is another argument against the running stitch. Serosa is approximated to serosa, so that no irregular spaces are left. A fine deposition of fibrin seals off the interspaces and produces the most rapid and effective regeneration of tissue. Nicholas Senn,[33] Edward Martin, J. B. Murphy, and others, at the turn of the century, pointed out the great danger of obstruction from too much inversion of the free ends of the gut wall. Murphy demonstrated that a broad serous approximation is not necessary, and that the smaller the bite, the smaller the diaphragm will be.

The more one sutures, the more one strangulates and devascularizes the gut. This leads to leakage at the suture line. There is no need for many sutures, but there is great need for well-disposed sutures (two layers). Excessive zeal in suturing the colon endangers a blood supply which at best is somewhat limited. Small areas of necrosis may develop at the suture line. This devitalization of tissue by strangulation in the field of the ever-present anaerobic bacteria of the colon may encourage a spreading gangrene. Therefore, the use of multiple (three or more) rows of continuous sutures (in the hope that if two are good, more are better) is not only a misconception of the function of suturing and no safeguard at all, but is frequently the instigator of fatal late leaks. The continuous suture stops the blood supply to the cut margins of the colon, and it is on these devitalized margins that the anaerobes flourish.

Safety in colon surgery depends as much upon the integrity of the blood supply as it does on the immediate security against leaks. However, both may be obtained by making an airtight or watertight closure which needs no more than two rows of interrupted sutures for success. The maintenance of sufficient blood supply is the warp and accurate mucosal apposition the woof of a successful anastomosis. Tension at the suture line should be avoided by adequate mobilization of the colon. There should be no pull on the suture line in the long axis of the colon, and what drag there is should be distributed equally around the circumference of the bowel. Tension on the suture line produced by postoperative gaseous distention is prevented by continuous Levine tube suction and the judicious use of the rectal tube. Further, the

application of fine interrupted sutures produces a minimum of tissue devitalization and permits the blood to reach the *fresh, cut noncrushed* margins of the bowel between the interrupted sutures, thus minimizing the danger of necrosis.

Safety in colon anastomosis also depends on the avoidance of crushing or devitalizing tissue in the suture line, and this avoidance is an outstanding feature of the open method of anastomosis which employs fine interrupted sutures throughout.

DISCUSSION

There is no attempt here to consider operability rates. A selected series of cases of resectable carcinoma of the colon is presented. The series, however, demonstrates that in cases with no obstruction, resection with primary anastomosis is the procedure of choice (our preference for the open method of anastomosis using two rows of interrupted sutures has been indicated). Further, most patients with partial or even complete obstruction under proper preoperative preparation may become fortunate candidates for resection and primary anastomosis.

In one case carcinoma of the transverse colon was discovered during an exploration of gastric carcinoma. Both the gastric resection and the segmental resection with primary open anastomosis of the transverse colon were performed simultaneously. Once an asymptomatic carcinoma of the sigmoid was discovered during an operation for total hysterectomy. This was nonobstructive and was resected segmentally immediately with primary open anastomosis.

Of the thirty-four cases, four were carcinoma of the right colon, three of the transverse colon, two of the rectosigmoid, one of the splenic flexure, and twenty-two of the sigmoid.

The changing history of resections for carcinoma of the colon has been discussed with emphasis on the modern trend of primary resection. This method flourishes only through the use of the newer concepts of physiology and biochemistry as applied to the pre- and postoperative management of the surgical patient. Some arguments for the *open* and against the *closed* methods of anastomosis are presented.

CONCLUSION

The shortened hospital stay, the elimination of multiple operations, the savings in time, expense, and psychologic trauma, together with the low mortality (two deaths) in thirty-four cases make the procedure of resection with primary open anastomosis one of choice, or at least one to be recommended highly in resectable, nonobstructive carcinoma of the colon.

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THE TREATMENT OF ACUTE APPENDICITIS IN A CLOSED CITY

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WHEN Reginald Fitz, Shattuck Professor of Pathological Anatomy in the Harvard Medical School, in 1886 first read his paper on "Perforating Inflammations of the Vermiform Appendix" at a meeting of the Association of American Physicians, he gave to the medical world its first clear-cut description of the pathologic process, the symptoms, the clinical findings, and suggested treatment of a disease which, although previously described, had not been clearly understood until that time, and as a result, not properly treated.

Although thousands of papers have been presented on this subject since then, little has been added to his original description and advice. Mortality statistics in this disease have been reduced since that time with the advances of surgery and its technique. In recent years chemotherapy with the sulfonamide drugs and penicillin have lowered still further our mortality in appendicitis, especially those cases with perforation and peritonitis. It is not my purpose in this paper to present anything new in the way of diagnosis, technique, or chemotherapy, but to discuss the treatment of appendicitis, and the success which was attained in a closed city where such a disease could be treated in its most ideal manner. The early recognition and diagnosis of appendicitis as described by Fitz, and immediate operation once the diagnosis is made as suggested by him and a contemporary surgeon of his time, Alfred Worcester, still stand paramount today as much as in 1886 in the successful treatment of appendicitis.

To quote a few sentences from Fitz's paper and some remarks of his colleague, Worcester:

Fitz recorded "A simple catarrhal appendicitis is to be recognized anatomically, but it is doubtful whether its clinical appreciation is possible. This appendicitis, in the absence of a concretion or foreign body, may progress toward ulceration, even to peritonitis, which may terminate fatally. In the presence of a foreign body or concretion, these events are of likely occurrence. On the one hand, the inflammation may result in the more or less complete obliteration of the canal of the appendix with or without circumscribed dilation. On the other, the ulcerative process becomes associated with a necrosis of the wall, a peritonitis, usually circumscribed at the onset, and perforation."

In respect to diagnosis after discussing the obscurity and variance in appendicitis he stated, "The presence, therefore, of the symptoms now to be mentioned in whom the history of one and particularly several such attacks is to be obtained, is of marked importance in aiding in diagnosis." He found, "that the majority of cases of resulting peritonitis began in the second, third, and fourth days after the inflammation of the appendix is established."

Worcester, who became an advocate of immediate operation as soon as a diagnosis could be made, maintained that "it is impossible to tell what cases are going to be bad." Also, he thought "that the physician should from the begin-

Read at a meeting of the Tennessee State Medical Association, April, 1946.
Received for publication, April 30, 1946.

ning, place the responsibility upon the surgeon—because, the end of the first day is later than the end of the first week in some cases.''

At the closed, wartime, secret atomic city of Oak Ridge, Tenn., the situation has been unique and unusual. The results in acute surgical conditions of the abdomen, especially acute appendicitis, have been exceptionally good. It is felt that good results have been achieved because of an unusual setup by which it has been possible to treat such a disease in its ideal manner. From December, 1943, to December, 1945, the surgical department has done 357 appendectomies for appendicitis with no mortalities. Oak Ridge has been a closed city of 25,000 to 75,000 population with a limited and centralized medical personnel. The personnel for the greater part has been a group of men trained in their various specialities. Consultation by men trained in surgery, medicine, pediatrics, and gynecology has been available for each and every case and at any time. A call rotation has permitted surgery at any time of the day or night without undue strain on any one surgeon. In short, it has been possible to carry out, idealistically, the treatment of appendicitis in a city of all people—not the rich—not the poor—not the whites—not the colored—but all in the same manner.

Staff.—The 357 appendectomies were performed or assisted in by 10 surgeons; 352 of these were participated in by a limited group of 6 surgeons (Table I).

TABLE I

SURGEON	APPENDECTOMIES	
A	44	
B	72	
C	69	352 or 98.6%
D	45	
E	65	
F	57	
G	2	
H	1	
I	1	
J	1	
Total	357	

DEFINITIONS

Of the 357 cases, pathologic findings were reported in all but 13. As will be seen later, because of the close correlation between operative findings and the pathologic findings, these were included in the subsequent statistics according to their operative reports, namely, 8 cases of acute appendicitis and 5 cases of normal appendices.

Acute Suppurative or Gangrenous Appendicitis.—One group includes those appendices found on pathologic examination to have suppurative inflammation with infiltration of polymorphonuclear cells invading the walls or an acutual necrosis of the walls of the appendices.

Perforated Appendix With Peritonitis.—One group includes those gangrenous appendices which have actually sustained a perforation of the walls, with pus in the peritoneal cavity either free (generalized), or walled off (localized or abscess). It does not represent those cases which show a localized peritonitis as a result of contiguousness to an inflamed organ, nor that group in which there is a clear but cell-containing fluid in the peritoneal cavity.

Subacute, Recurrent, Chronic, Sclerotic.—One group includes those appendices which by means of cellular elements or fibrotic changes seen in the walls show signs of subacute or receding inflammation or changes resulting from previous inflammatory processes.

Normal Appendices.—One group includes those appendices which show no signs of inflammatory process recent or past and are essentially normal in all respects.

SEX

Of the 357 appendectomies, 200 were performed on males and 157 on females.

Males.—Of the 200 males, 123, or 61.5 per cent of them, had pathologically acute suppurative or gangrenous appendicitis. Seventeen, or 8.5 per cent of them, had perforated appendicitis with peritonitis; of which 7, or 3.5 per cent, had general peritonitis and 10, or 5.0 per cent, had local peritonitis or abscess. Thirty-four, or 17.0 per cent, had subacute appendicitis or sclerotic appendix and 26, or 13 per cent, had normal appendices.

Females.—Of the 157 females, 54, or 34.4 per cent, had acute, suppurative or gangrenous appendicitis; 6, or 3.8 per cent, had perforated appendicitis with peritonitis, of which 5, or 3.1 per cent, had general peritonitis and 1, or 0.7 per cent, had local peritonitis or abscess; 44, or 28.0 per cent, had subacute appendicitis or sclerotic appendix and 53, or 33.8 per cent, had normal appendices.

TABLE II. SEX DISTRIBUTION

357 Cases

Males	200 cases	56%
Females	157 cases	44%

	Acute, suppurative		*Perforated with peritonitis*				*Subacute sclerotic*		*Normal*		*Total*	
			General		*Local*							
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Males	123	61.5	7	3.5	10	5.0	34	17.0	26	13.0	200	100
Females	54	34.4	5	3.1	1	0.7	44	28.0	53	33.8	157	100

Pathologically Involved Appendices
278 cases—78%

	Acute, suppurative or perforated		*Subacute, sclerotic*		*Total*	
Male	140	(70.0%)	34	(43.5%)	174	62.6%
Female	60	(30.0%)	44	(56.5%)	104	37.4%
	200		78			

Normal Appendices
79 cases—22%

Males	26 cases	32.9%
Females	53 cases	67.1%

Of the acute suppurative, gangrenous, and perforated appendices, 70.0 per cent were in males and 30.0 per cent in females. Of the subacute sclerotic group, 43.5 per cent were in males and 56.5 per cent in females. Of the normal appendices, 32.9 per cent were in males and 67.1 per cent in females (Table II).

PREVIOUS ATTACKS

In review of the histories of these cases definite information concerning previous attacks could be recorded in only 195 cases. In acute, suppurative,

gangrenous, or perforated appendicitis 68.6 per cent of the patients had had previous attacks. In subacute recurrent or sclerotic appendicitis 76.9 per cent had had previous attacks. In appendices found to be normal 70.2 per cent gave histories of having similar symptoms previously (Table III).

TABLE III. HISTORY OF PREVIOUS ATTACKS

	NONE			ONE OR MORE				NO REPORT			
	M	F	T	M	F	T	PER CENT	M	F	T	TOTAL
Acute, suppurative perforated	25	5	30	45	21	66	68.6	71	33	104	200
Subacute, recurrent sclerotic	7	5	12	18	22	40	76.9	9	17	26	78
Normal	8	6	14	4	29	33	70.2	13	19	32	79
Total	40	16	56	67	72	139		93	69	162	357

It will be noted that in acute appendicitis there is a high percentage of previous attacks and this is especially so in those cases which show signs of changes from previous inflammation.

It is also interesting to note that 70.2 per cent of those patients found to have normal appendices also gave histories of previous attacks of similar symptoms, which adds to the difficulties in differentiating these from true appendicitis in the clinical diagnosis. However, it is evident that appendicitis is a disease which recurs and that a history of previous attacks or symptoms is significant.

From here on the discussion will not include the group of 79 cases which were found to be normal on pathologic examination and only the 278 cases found to have pathologic involvement will be dealt with. However, I wish to comment that, in the successful treatment of appendicitis, a certain number of abdomens will have to be opened in exploration when acute appendicitis cannot be ruled out definitely by clinical means. Some of these were surgical abdomens although the appendix was found to be normal. Five cases of Meckel's diverticulum, one with perforation, are in this group. An abscess of the wall of the cecum is another case and a perforated peptic ulcer is still another. This is especially true in women where the differentiation between pelvic pathology and acute appendicitis is almost impossible at times.

SEASONAL DISTRIBUTION

Findings show that appendicitis has no seasonal variations. It occurs with about equal frequency during all seasons of the year and bears no particular relation to the seasons for upper respiratory disturbances or enteritis (Table IV).

TABLE IV. SEASONAL DISTRIBUTION OF APPENDICITIS

SEASON	ACUTE SUPPURATIVE PERFORATED		SUBACUTE SCLEROTIC		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Spring (March, April, May)	47	23.5	23	29.5	70	25.2
Summer (June, July, Aug.)	51	25.5	24	30.8	75	27.0
Fall (Sept., Oct., Nov.)	49	24.5	21	26.9	70	25.2
Winter (Dec., Jan., Feb.)	53	26.5	10	12.8	63	23.0

TABLE V. DURATION OF SYMPTOMS

DURATION	MALES	FEMALES	TOTAL	PER CENT
Acute, Suppurative or Gangrenous Appendicitis				
2 hr. or under	1	1	2	1.1
2-8 hr.	27	8	35	19.8
8-16 hr.	36	20	56	31.6
16-24 hr.	16	8	24	13.6—66.1
24-36 hr.	17	5	22	12.4—78.5
36-48 hr.	5	2	7	4.0
48-72 hr.	9	6	15	8.5
72-96 hr.	6	3	9	5.1
4 days and over	6	1	7	4.01
Total	123	54	177	

	GENERAL PERITONITIS		LOCAL PERITONITIS			
DURATION	MALES	FEMALES	MALES	FEMALES	TOTAL	PER CENT
Perforated Appendicitis With Peritonitis						
2-8 hr.	1	0	1	0	2	8.7
8-16 hr.	0	0	1	0	1	4.3
16-24 hr.	0	2	1	0	3	13.0—26.1
24-36 hr.	3	1	2	0	6	26.1—52.2
36-48 hr.	0	1	0	0	1	4.3
48-72 hr.	1	1	1	1	4	17.4
72-96 hr.	1	0	1	0	2	8.7
4 days and over	1	0	3	0	4	17.4
Total	7	5	10	1	23	

DURATION	MALES	FEMALES	TOTAL	PER CENT
Subacute Recurrent or Sclerotic Appendicitis				
2 hr. or under	2	0	2	2.6
2-8 hr.	5	6	11	14.1
8-16 hr.	4	4	8	10.3
16-24 hr.	4	2	6	7.7—24.6
24-36 hr.	7	11	18	23.1—57.6
36-48 hr.	1	1	2	2.6
48-72 hr.	2	7	9	10.5
72-96 hr.	3	4	7	9.0
4 days and over	4	4	8	10.3
Interval	3	4	7	9.0

DURATION OF SYMPTOMS

As mentioned previously one of the most important factors in the successful treatment of acute appendicitis is the possibility of being able to see a patient early in the course of the disease. This allows early recognition or diagnosis and prompt surgical removal.

Of all the patients in this series, 66.1 per cent with acute or suppurative appendicitis were seen within the first twenty-four hours, and within the first thirty-six hours this figure jumped up to 78.5 per cent. Of the patients with perforated appendicitis with peritonitis, 26.1 per cent were seen within twenty-four hours of the onset and 52.2 per cent were seen within thirty-six hours. It can be seen that even a delay of twelve hours in a progressing suppurative or gangrenous appendicitis can increase markedly the percentage of perforation. Of the subacute or sclerotic group the distribution of the duration of symptoms was more variable as might be suspected (Table V).

AGE DISTRIBUTION

The age distribution showed nothing unusual to the general run for acute appendicitis. 72.5 per cent of the cases of acute suppurative or perforated

appendicitis occurred in the age group of 30 years and under, with 54.5 per cent of all the acute suppurative or perforated cases occurring in the 16 to 30 year group. Also, the subacute recurrent or sclerotic cases are most common in these age groups with 74.4 per cent of them occurring at the age of 30 years or under. They are, however, less common in the first three age groups up to 16 years of age. The youngest patient was 3 years old and the oldest 66 (Table VI).

TABLE VI. AGE DISTRIBUTION OF APPENDICITIS

	ACUTE SUPPURATIVE		PERFORATED WITH PERITONITIS					
			GENERAL		LOCAL			
AGE GROUP	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	TOTAL	PER CENT
3-5 yr.	2	0	1	0	0	0	3	1.5
6-10 yr.	8	5	2	0	0	0	15	7.5
11-15 yr.	14	3	0	1	0	0	18	9.0
16-20 yr.	13	15	0	1	1	0	30	15.0
21-25 yr.	26	12	0	0	1	1	40	20.0
26-30 yr.	27	8	1	0	3	0	39	19.5—72.5
31-35 yr.	11	5	1	0	3	0	20	10.0
36-40 yr.	9	3	1	0	0	0	13	6.5
41-45 yr.	7	0	0	1	1	0	9	4.5
46-50 yr.	6	2	0	0	1	0	9	4.5
56-60 yr.	0	1	1	1	0	0	3	1.5
61-65 yr.	0	0	0	0	0	0	0	0.0
66 yr. and over	0	0	0	1	0	0	1	0.5
Total	123	54	7	5	10	1	200	

AGE GROUP	MALES	FEMALES	TOTAL	PER CENT
Subacute Sclerotic Appendicitis				
3-5 yr.	0	0	0	0.0
6-10 yr.	1	2	3	3.8
11-15 yr.	1	1	2	2.6
16-20 yr.	5	16	21	26.9
21-25 yr.	6	17	23	29.5
26-30 yr.	6	3	9	10.5—74.4
31-35 yr.	5	1	6	7.7
36-40 yr.	5	2	7	9.0
41-45 yr.	1	2	3	3.8
46-50 yr.	1	0	1	1.3
51-55 yr.	2	0	2	2.6
56-60 yr.	0	0	0	0.0
61-65 yr.	1	0	1	1.3
66 yr. and over	0	0	0	0.0
Total	34	44	78	

TREATMENT

Incisions.—McBurney incisions were used in 255 cases, 167 times in males and 88 times in females. Right rectus incisions were used in 90 cases, 29 times in males and 61 times in females. Various other incisions were used in the remaining 12 cases (Table VII).

Treatment of the Appendical Stump.—In those cases reported the appendical stump was inverted with a purse-string suture in 188 cases or 58.4 per cent, and merely tied off without inversion in 134 cases or 41.6 per cent (Table VIII).

Drainage of the Abdomen.—The abdomen was drained in twenty-four patients. Seven of these were in nonperforated cases where it was used as a

TABLE VII. OPERATIVE INCISIONS

	MALE	PER CENT	FEMALE	PER CENT	TOTAL	PER CENT
McBurney	167	83.5	88	56.1	255	71.4
Right rectus	29	14.5	61	38.9	90	25.2
Midline	0	0.0	2	1.3	2	3.4
Gridiron	1	0.5	1	0.6	2	
Left rectus	0	0.0	2	1.3	2	
Herniorrhaphy	2	1.0	0	0.0	2	
No report	1	0.5	3	1.9	4	
Total	200	100.0	157	100.0	357	100.0

TABLE VIII. TREATMENT OF THE APPENDICAL STUMP

Inverted with purse string	188
Tied, with no inversion	134
No report	35
Total	357

safety measure. In the perforated cases drainage was used seventeen times, or 73.9 per cent of the cases. It was used seven times in perforated appendicitis with general peritonitis, or in 58.1 per cent of these cases, and ten out of eleven times in the cases of perforation with local peritonitis or abscess, or in 90.0 per cent of these cases. In a total of six cases of perforated appendicitis with peritonitis closure was without drainage, five with general peritonitis and one with local peritonitis (Table IX).

TABLE IX. DRAINAGE OF THE ABDOMEN

	DRAINED	PER CENT	NOT DRAINED	PER CENT
Acute, suppurative gangrenous, *not* perforated	7	4.1	163	95.9
Perforated appendicitis with local peritonitis	10	90.9	1	9.1
Perforated appendicitis with general peritonitis	7	58.1	5	41.9

The Use of Chemotherapy in Appendicitis.—In discussing the use of chemotherapy only the acute suppurative, gangrenous, and perforated cases will be included, namely, those cases in which we might look for something significant in the way of benefit received in the form of lowered mortality or morbidity in actual suppurative conditions. Of the 200 cases of acute suppurative or gangrenous appendicitis and perforated appendices with peritonitis 117 patients, or 58.5 per cent, received chemotherapy in some form, and 83, or 41.5 per cent, received no chemotherapy whatever. Of these 117 patients, 90 received sulfonamide alone, 7 received penicillin alone, and 20 received combinations of sulfonamide and penicillin (Table X).

COMPARISON OF CLINICAL DIAGNOSIS, OPERATIVE FINDINGS, AND PATHOLOGIC DIAGNOSIS

Of the 322 cases diagnosed clinically as acute appendicitis or perforated appendicitis with peritonitis, 221 were so diagnosed on operation, of which 192 were so diagnosed pathologically. In other words 192, or 86.8 per cent, of those

TABLE X. CHEMOTHERAPY USED

	ACUTE SUPPURATIVE	PERFORATED PERITONITIS		TOTAL
Sulfa Alone				
Locally	58	1		59
Systemically	6	3		9
Locally and systemically	17	5		22
Total	81	9		90
Penicillin Alone				
Locally	0	0		0
Systemically	6	0		6
Locally and systemically	1	0		1
Total	7	0		7
Sulfa and Penicillin Combined				
Locally	0	0		0
Systemically	4	2		6
Locally and systemically	4	10		14
Total	8	12		20
			(58.5%)	117
No Chemotherapy	81	2	(41.5%)	83
Total				200

appendices diagnosed at the operating table as being acute or suppurative appendicitis were so found on pathologic examination.

Of the ninety-nine cases called normal at the operating table only seventy-four, or 75.7 per cent, were diagnosed as showing no pathology on microscopic examination. It was because of this close correlation between the pathologic diagnosis and the operative diagnosis that the thirteen cases in which no pathologic report could be found were included in the final statistics of these cases, assigning them according to their operative findings as eight cases of acute appendicitis and five normal appendices (Table XI).

HOSPITAL STAY OR MORBIDITY

Before starting the discussion on hospital stay it is to be considered that the greater part of those patients receiving chemotherapy were sicker clinically

TABLE XI. COMPARISON OF CLINICAL DIAGNOSIS, OPERATIVE FINDINGS, AND PATHOLOGIC DIAGNOSIS

	CLINICAL DIAGNOSIS	OPERATIVE FINDINGS	PATHOLOGIC DIAGNOSIS
Acute suppurative gangrenous	311	198	192
Perforated with general peritonitis	8	12	---
Perforated with local peritonitis	3	11	---
Subacute recurrent sclerotic	35	28	78
Normal	0	99	74
No report	0	9	13
Total	357	357	357

357 Appendectomies
278 or 78 per cent pathologically involved
79 or 22 per cent normal
278 Pathologically involved appendices
177 or 63.7 per cent acute suppurative appendicitis
23 or 8.3 per cent perforated appendicitis with peritonitis
78 or 28.0 per cent subacutely involved or showing sclerotic changes

TABLE XII. AVERAGE HOSPITAL STAY OF APPENDECTOMY PATIENTS WITH PATHOLOGIC DIAGNOSIS OF NORMAL APPENDIX

	MC BURNEY INCISION (46 CASES)	RIGHT RECTUS INCISION (30 CASES)
Average hospital stay	7.2 days	9.5 days
Shortest stay	3 days	6 days
Longest stay	21 days	16 days

from the onset, especially those who received the drugs systemically. In analyzing the hospital stay of these patients the type of incision used is taken into consideration, the part which chemotherapy may or may not have played in lessening their morbidity, and also those cases of peritonitis in which drainage was or was not used. The discussion will deal with those cases of acute suppurative appendicitis and perforated appendicitis with peritonitis. However, for comparison the average hospital stay of those patients in whom the appendix was found to be normal or subacutely inflamed or sclerotic will be presented first (Tables XII and XIII).

TABLE XIII. AVERAGE HOSPITAL STAY OF APPENDECTOMY PATIENTS WITH PATHOLOGIC DIAGNOSIS OF SUBACUTE APPENDICITIS OR SCLEROTIC APPENDIX

	MC BURNEY INCISION (45 CASES)	RIGHT RECTUS INCISION (29 CASES)
Average hospital stay	7.4 days	10.5 days
Shortest stay	2 days	7 days
Longest stay	27 days	14 days

Patients With Acute Suppurative or Gangrenous Appendicitis.—In acute suppurative or gangrenous appendicitis the average length of hospital stay for all patients receiving chemotherapy of any sort was for those with McBurney incisions 7.7 days and for those with right rectus incisions 9.0 days. In those patients receiving *no* chemotherapy whatsoever, those with McBurney incisions stayed 6.5 days and those with right rectus incisions 8.0 days. The results found in breaking down these figures are shown in Table XIV.

Patients With Perforated Appendicitis and Peritonitis in Relation to Drainage of the Abdomen.—Cases of perforated appendicitis and peritonitis will

TABLE XIV. AVERAGE HOSPITAL STAY IN CASES OF ACUTE SUPPURATIVE OR GANGRENOUS APPENDICITIS

	NUMBER OF CASES	MC BURNEY INCISION (DAYS)	RIGHT RECTUS INCISION (DAYS)
Sulfa Drug Alone	81		
Locally	58	6.6	8.8
Systemically	6	9.7	----
Locally and systemically	17	8.6	12.0
Penicillin Alone	7		
Systemically	6	8.0	11.0 (1 case)
Locally and systemically	1	6.0	----
Sulfa and Penicillin	8		
Systemically	4	7.8	----
Locally and systemically	4	16.0	10.0 (1 case)
All patients with chemotherapy	95	7.7	9.0
No chemotherapy	81	6.5	8.0

TABLE XV. AVERAGE HOSPITAL STAY IN CASES OF PERFORATED APPENDICITIS WITH PERITONITIS IN RELATION TO DRAINAGE

	DRAINED	NOT DRAINED
General Peritonitis (12 cases)		
McBurney Incisions (9 cases)	6 cases	3 cases
Shortest stay	8 days	6 days
Longest stay	23 days	18 days
Average stay	13.8 days	10.3 days
Right Rectus Incisions (3 cases)	2 cases	1 case
Shortest stay	15 days	
Longest stay	19 days	
Average stay	17 days	9 days
Local Peritonitis (11 cases)		
McBurney Incisions (7 cases)	6 cases	1 case
Shortest stay	7 days	
Longest stay	23 days	
Average stay	12.7 days	11 days
Right Rectus Incisions (4 cases)	4 cases	0 cases
Shortest stay	10 days	-
Longest stay	19 days	-
Average stay	15 days	-

be discussed first in relation to drainage of the abdomen and then chemotherapy. In *general peritonitis* drainage was carried out in eight patients, with an average hospital stay of 13.8 days for those with McBurney incisions and 17.0 days for those with right rectus incisions. Drainage was not carried out in four patients, with an average hospital stay of 10.3 days for those with McBurney incisions and 9.0 days (one case) for those with right rectus incisions. In *local peritonitis* or abscess drainage was carried out in ten patients with an average hospital stay of 12.7 days for those with McBurney incisions and 15.0 days for those with right rectus incisions.

Drainage was not carried out in one patient with a McBurney incision who remained in the hospital for eleven days (Table XV).

Patients With Perforated Appendicitis With Peritonitis in Relation to Chemotherapy.—Cases of perforated appendicitis with peritonitis in relation to chemotherapy also fall into two groups. Of the twelve cases of *general peri-*

TABLE XVI. AVERAGE HOSPITAL STAY IN CASES OF PERFORATED APPENDICITIS WITH GENERAL PERITONITIS

	NUMBER OF CASES	SHORTEST STAY (DAYS)	LONGEST STAY (DAYS)	AVERAGE STAY (DAYS)
McBurney Incision Cases				
Sulfa drug locally	1	--	--	7.0
Sulfa locally and systemically	2	6	18	12.0
Sulfa and penicillin locally and systemically	5	9	23	15.0
Average length of stay with chemotherapy	8			13.25
Average length of stay with *no* chemotherapy	1			8.0
Right Rectus Incision Cases				
Sulfa drug systemically	1	--	--	15.0
Sulfa and penicillin locally and systemically	2	9	19	14.0
Average length of stay with chemotherapy	3			14.3
There were no cases in which *no* chemotherapy was used				

tonitis, chemotherapy was used in eleven cases and no chemotherapy in one (Table XVI). Of the eleven cases of *local peritonitis or abscess,* chemotherapy was used in ten cases (Table XVII).

It is impossible, of course, to make any significant comparison of the patients with perforated appendicitis with peritonitis who received no chemotherapy with those who did, as this group consisted of only two cases. However, it is felt that the morbidity of those patients with perforated appendicitis with peritonitis who received chemotherapy, namely, 13.25 hospital days and 14.3 hospital days with McBurney and right rectus incisions, respectively, in general

TABLE XVII. AVERAGE HOSPITAL STAY IN CASES OF PERFORATED APPENDICITIS WITH LOCAL PERITONITIS OR ABSCESS

	NUMBER OF CASES	SHORTEST STAY (DAYS)	LONGEST STAY (DAYS)	AVERAGE STAY (DAYS)
McBurney Incision Cases				
Sulfa drug systemically	2	11	23	17.0
Sulfa locally and systemically	1	--	--	17.0
Sulfa and penicillin systemically	2	7	9	8.0
Sulfa and penicillin locally and systemically	2	10	10	10.0
Average length of stay with chemotherapy	7			12.4
There were no cases in which *no* chemotherapy was used				
Right rectus incision cases				
Sulfa drug systemically	1	--	--	10.0
Sulfa locally and systemically	1	--	--	19.0
Sulfa and penicillin locally and systemically	1	--	--	17.0
Average length of stay with chemotherapy	3			16.7
Average length of stay with *no* chemotherapy	1			10.0

TABLE XVIII. OVER-ALL COMPARISON OF THE AVERAGE HOSPITAL STAY OF ALL PATIENTS WHO HAD APPENDECTOMIES

	MC BURNEY INCISIONS		RIGHT RECTUS INCISIONS	
	CASES	AVERAGE STAY (DAYS)	CASES	AVERAGE STAY (DAYS)
Normal appendices	46	7.2	30	9.5
Subacute sclerotic appendicitis	45	7.4	29	10.5
Acute suppurative appendicitis with *no* chemotherapy	68	6.5	13	8.0
Acute suppurative appendicitis with chemotherapy	82	7.7	14	9.0
Perforated appendicitis, general peritonitis with drainage	6	13.8	2	17.0
Perforated appendicitis, general peritonitis with *no* drainage	3	10.3	1	9.0
Perforated appendicitis, general peritonitis with chemotherapy	8	13.25	3	14.3
Perforated appendicitis, general peritonitis with *no* chemotherapy	1	8.0	0	---
Perforated appendicitis, local peritonitis with drainage	6	12.7	4	15.0
Perforated appendicitis, local peritonitis with *no* drainage	1	11.0	0	---
Perforated appendicitis, local peritonitis with chemotherapy	7	12.4	3	16.7
Perforated appendicitis, local peritonitis with *no* chemotherapy	0	---	1	10.0

peritonitis, and 12.4 hospital days and 16.7 hospital days with McBurney and right rectus incisions, respectively, in local peritonitis or abscess, is low for such a serious complication of appendicitis and that the chemotherapy as well as early operation has played a large part in this low morbidity and no fatalities (Table XVIII).

CONCLUSIONS

1. The closed city of Oak Ridge has afforded an unusual and an ideal opportunity for the treatment of such a disease as acute appendicitis. The greater majority of the cases, acute, recurrent, and perforated have been seen early in the course of the disease or the particular attack. Consultation has been available, with men trained in their various specialities, at all times in the questionable diagnostic cases. Prompt surgical treatment has been carried out by a constant group of surgeons.

2. It is as true today as it was in 1886, when first brought out by Reginald Fitz, that the most important factor in the treatment of the disease of acute appendicitis is the early recognition and diagnosis of the condition and its prompt surgical treatment. It is as important that the public be educated in the symptoms of this disease as in the infectious and contagious diseases stressed in preventive medicine. It is important that the physician be consulted early and that he recognize the disease which at times can be very vague and deceiving in story and findings. It is important that, in cases in which the diagnosis had not been definitely established, the patient be watched carefully and frequently, as changes in the clinical findings can occur within a short period of time as can the pathologic state of the appendix.

3. In the successful treatment of acute appendicitis a certain number of normal appendices will be removed and exploration of the abdomen done. This is especially true in women in whom pelvic disturbances so simulate appendicitis in their clinical findings that differentiation is impossible. However, the error is greater if one "watches" than if one "looks" when all diagnostic aids have been exhausted and the differentiation cannot be made.

4. Appendicitis is a recurring disease with a history of previous attacks, which in our series was found in 71.6 per cent of the cases; "it is impossible to tell which cases are going to be bad."

5. Chemotherapy, employing sulfonamide drugs alone or in conjunction with penicillin, especially used systemically, has been a definite aid in producing no mortalities and an unusually low morbidity in this series of perforated appendicitis with peritonitis.

6. Chemotherapy does not offer as much in the cases of acute appendicitis without perforation. Local use of the sulfonamide drugs (penicillin not used alone) adds little, if anything, to lessening morbidity or preventing complications. Systemically, both are of value in the more acutely ill patients or toxic cases and in those cases complicated by other infections, as respiratory, kidney, or pelvic.

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INCOMPLETE REMOVAL OF THE CYSTIC DUCT AS A FACTOR IN PRODUCING POSTCHOLECYSTECTOMY COMPLICATIONS

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WHENEVER the gall bladder becomes diseased, the pathologic process invariably spreads to the cystic duct and may often involve other biliary radicals. Frequently it is the disturbance of cystic duct function which not only aggravates the existing cholecystopathy but may initiate the distressing symptoms which require remedial surgical therapy. For example, a mildly diseased gall bladder may harbor a small calculus without provoking distressing symptoms but if that stone becomes impacted in the cystic duct then acute biliary colic may ensue. Again, a gall bladder may possess normal secretory and absorptive functions but kinks, adhesions, or anatomic deformities of the cystic duct can so obstruct the flow of bile that disconcerting syndromes result.

If this premise be correct then the entire cystic duct should be removed along with the diseased gall bladder. While most surgeons insist that they comply with rule, there are but few who appreciate how frequently it is violated. Beye,[2] in 1936, reported fourteen instances in which long residual cystic ducts had become so dilated as to resemble "reformed gall bladders," and they produced such serious disturbances as to necessitate secondary operations. Best & Hicken[1] emphasized the role of the "residual cystic duct" in maintaining persistent external biliary fistulas. Later, Macdonald,[6] in an exhaustive and scholarly paper, re-emphasized the fact that an infected cystic duct can produce a series of pathologic changes which may so interfere with choledochal functions as to require subsequent explorations.

Failure to appreciate anatomic abnormalities of the cystic duct contributes to its incomplete removal. Variations in its length, configuration, and relationship to the common hepatic bile duct are very common.

Normally the cystic duct is about 3 or 4 cm. in length and lies between the leaves of the gastrohepatic ligament where it unites with the common hepatic bile duct to form the choledochus (Fig. 1). Occasionally, however, the cystic duct may be short so that the gall bladder seems to empty directly into the common hepatic duct. On the other hand, it may be long and tortuous, thus presenting an S-shaped configuration (Fig. 2). At times the cystic duct passes mesially, as if to meet the common hepatic duct, but the two ducts descend together in a contiguous manner until they pass behind the duodenum, where they fuse to form a short, inaccessible common bile duct (Fig. 3). The cystic duct usually empties into the common hepatic duct on its lateral margin, forming an acute angle at their juncture. However, it may empty into the anterior, mesial,

Received for publication, April 3, 1946.

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Fig. 1.

Fig. 2.

Fig. 1.—The operative cholangiogram gives an accurate pattern of the entire biliary system and pancreatic ducts. Note how the cystic duct passes mesially toward the common hepatic bile duct, and then descends along its lateral margin before the two unite. If ligated near the gall bladder a long redundant cystic duct is left in situ.

Fig. 2.—A postoperative cholangiogram made by injecting a persistent external biliary fistula with diodrast. Observe the long, dilated, S-shaped cystic duct. This is a striking contrast to that shown in Fig. 1. Note the obstructing choledochal stone.

or posterior surface of the common hepatic duct. Macdonald[6] described an instance wherein the cystic duct passed behind the common hepatic duct so as to open into its mesial surface. Reference to Fig. 4 shows how easily ligatures can be placed around the abnormal cystic duct to leave a long redundant stump.

Any abnormalities of the cystic duct can be detected accurately by employing visualizing cholangiograms during the operation. This is accomplished by injecting a solution of 70 per cent diodrast* into the gall bladder lumen and then taking an x-ray view. As the gall bladder and associated biliary radicals will be filled with the contrast medium, an accurate roentgenographic pattern of their size, shape, and relationships will be obtained.

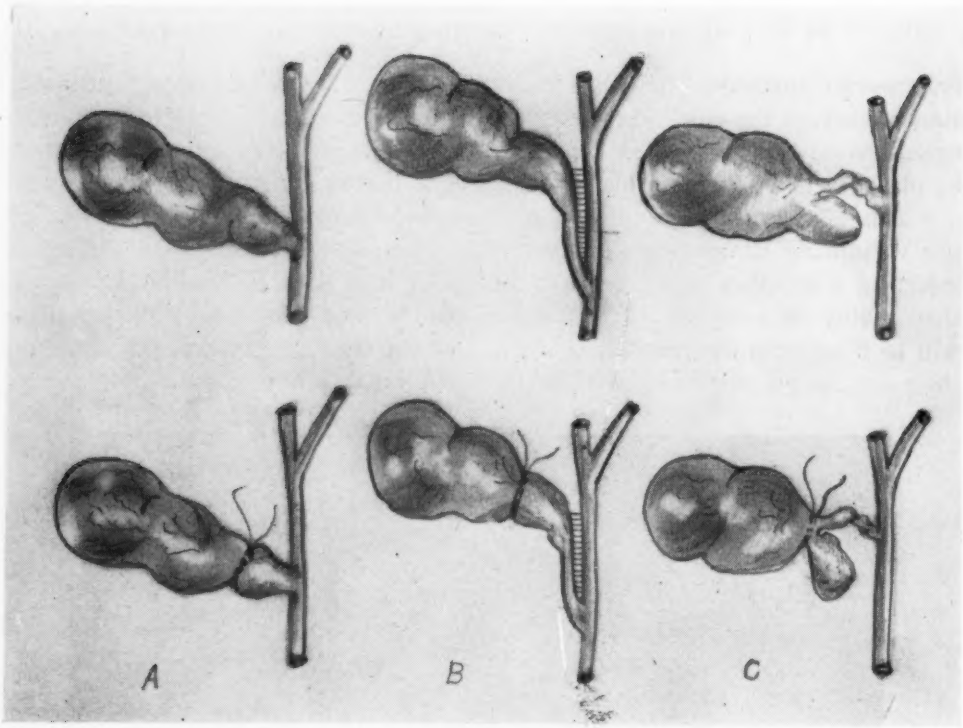
Fig. 3.—Observe how the cystic duct descends along the lateral margin of the common hepatic bile duct for a distance of 3 cm. before the two fuse.

Experience dictates that disturbing dysfunctions of the biliary tract often persist after a cholecystectomy. We have found that the irritative focus is frequently harbored in the remnant of the cystic duct. Corroborative evidence can best be given by submitting representative cases.

DILATATION OF THE RESIDUAL CYSTIC DUCT—"REFORMED GALL BLADDERS"

Beye[2] appreciated the fact that a long stump of the cystic duct is prone to become dilated as a result of the constant hydrostatic pressure from choledochal bile. The distended cystic ducts resembled small gall bladders and to them he gave the name reformed gall bladders. He admitted that this is not an accurate description of existing pathologic conditions, for the reformed gall bladders do

*Diodrast supplied by research Department, Winthrop Chemical Company, Inc., New York, N. Y.



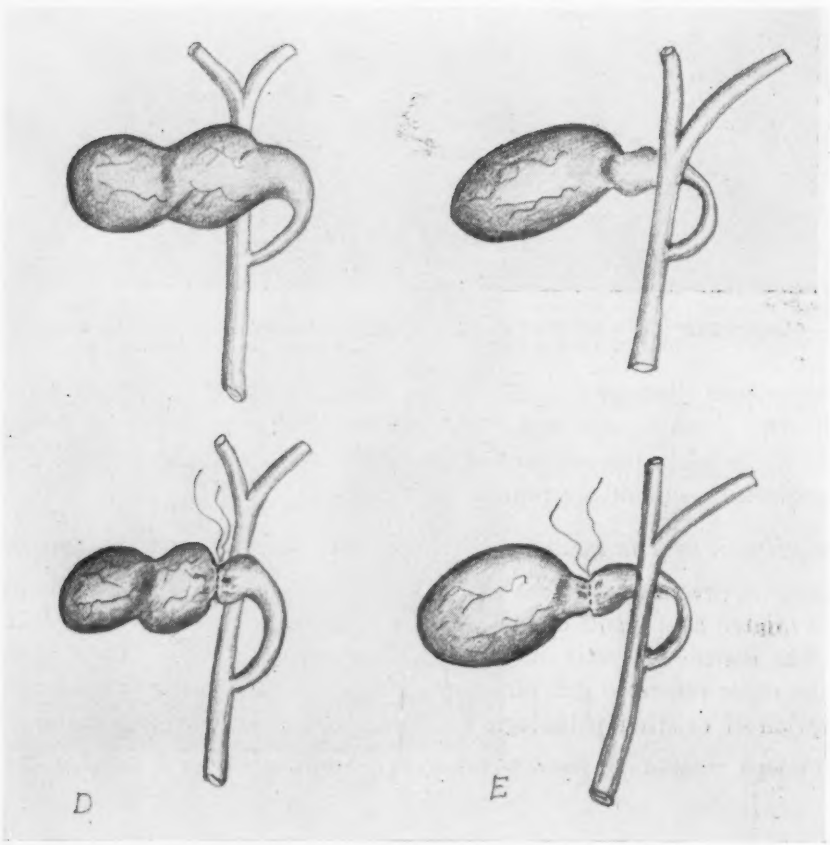


Fig. 4. *(For legend see opposite page.)*

not contain the mucosal or muscular components of the gall bladder. The dilated cystic duct, however, affords an excellent receptacle for bile, but lacking the contractile properties of the gall bladder, it cannot evacuate its contents into the common bile duct. This permits the stagnant bile to disintegrate, thereby favoring the formation of stones.

CASE 1.—F. B., a merchant, 66 years of age, had been bothered with "liver troubles" for a period of fifty years, the initial attack following a prolonged case of typhoid fever. A cholecystectomy was performed in May, 1920, following which he was well for eight years. A recurring jaundice aggravated by colicky pains compelled him to submit to a second exploration of the common bile duct on July 16, 1928. The operative records maintain that the

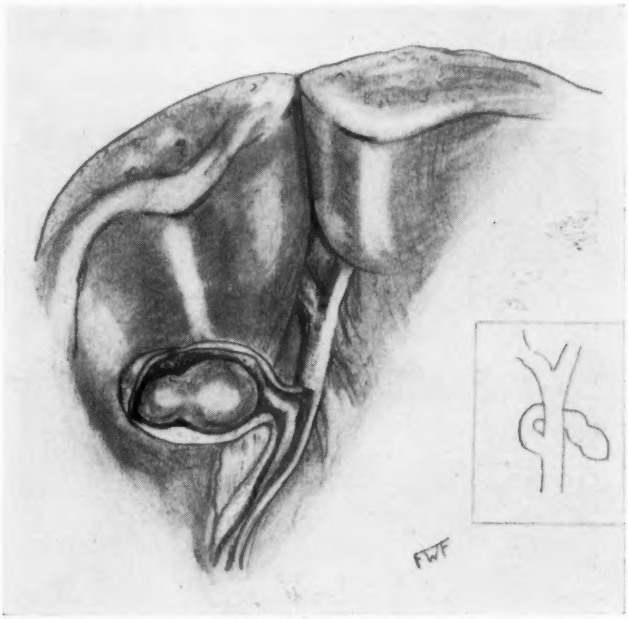


Fig. 5.—Insert shows how the cystic duct had herniated through the foramen of Winslow to project into the lesser omental cavity. The main drawing reveals how the cystic duct appeared after being delivered from the lesser omental cavity. Note how it resembles a reformed gall bladder. The impacted cystic duct stone produced a compressive mucocele which effectively obstructed the common hepatic bile duct.

"choledochus was normal and no cause of the obstructive jaundice was found." However, he continued to have intermittent episodes of jaundice with pronounced pains. On April 6, 1944, the abdomen was opened and an obstruction of the common hepatic bile duct was encountered. In order to determine the nature of this compressive mass a 22 gauge needle was inserted into it and, much to our surprise, we were able to aspirate 12 c.c. of white mucus. In the hope of determining the ramifications of the cystic mass it was injected with 12 c.c. of

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Fig. 4.—Schematic drawings representing a few of the more common anatomic variations of the cystic duct. If the ligature is placed in the usual position with reference to the common hepatic bile duct, the entire cystic duct, and in many cases a portion of the gall bladder, may be left in stiu.

A, Short cystic duct. Ligature includes a portion of the gall bladder and the entire cystic duct. *B*, Long, descending cystic duct. Ligature includes entire cystic duct. *C*, Normal cystic duct and dilated pouch of Hartmann. Ligature includes Hartmann's pouch and entire cystic duct. *D*, A long cystic duct passes anterior to the common hepatic duct before uniting with the mesial margin of the latter. Ligature includes the entire cystic duct. *E*, Cystic duct passes behind the common hepatic bile duct before uniting with its mesial margin. Ligature includes entire cystic duct.

70 per cent diodrast and a roentgenogram was taken. The resulting cholangiogram revealed the mass to be the dilated cystic duct, a portion of which had herniated through the foramen of Winslow and was protruding into the lesser omental cavity.

After the foramen of Winslow was enlarged by incision of its upper and lower margins, the cystic tumor was extracted from the lesser omental cavity. In Fig. 5 is shown how the incarcerated stone had produced a hydrops of the cystic duct, thus causing it to resemble a reformed gall bladder.

The manner in which the redundant cystic duct obtained access to the lesser omental cavity cannot be determined accurately. In all probability it was pushed through the foramen of Winslow during the process of "sponging the gall bladder fossa," at the primary operation. The residual stone so effectively obstructed the cystic duct that a mucocele developed. The abnormal position of the cystic mass permitted it to compress the terminal portion of the common hepatic bile duct. Excision of the cystic duct effected a cure which the two previous operations had been unable to accomplish. This demonstrates the value of cholangiography in determining anatomic abnormalities of the biliary radicals.

Fig. 6.—Cholangiogram made by injecting diodrast into a persistent external biliary fistula. The long S-shaped cystic duct is so dilated that it resembles a reformed gall bladder. Observe the impacted choledochal stone. The small stringlike trickle of diodrast passing through the ampulla of Vater signifies a compressive pancreatitis.

CASE 2.—Mrs. F. B., a housewife, 55 years of age, had had a cholecystectomy and several stones removed from the common bile duct. The resulting fistula drained bile for eight weeks. At this time a catheter was inserted into the draining fistula and 22 c.c. of diodrast were injected into the tube. The resulting cholangiograms outlined an enormously dilated choledochus which was partially occluded by a supra-ampullary stone. In Fig. 6 can be noted the thin thread of contrast media, which seeped around the choledochal stone to enter the

ampulla of Vater. This thread pattern is characteristic of an inflammatory pancreatitis. Following these injection studies, the draining fistula healed spontaneously and the patient was discharged by the attending physician.

Six weeks later she was readmitted to the hospital with an intense jaundice. At operation conditions were found as depicted by the previous cholangiograms. The long dilated stump of the cystic duct which resembled a small gall bladder was found to contain "biliary sand." The saccular cystic duct was removed and the choledochus was opened so that the impacted stone could be extracted. Ten days later the postoperative cholangiograms revealed that the pancreatitis had subsided, therefore the drainage tubes were removed. She has been free of all distress during the past two years.

CASE 3.—A farmer, 65 years of age, had had gallstones and gall bladder removed. Following this operation there had been a persistent drainage of bile from the sinus tract for ten weeks. When he was readmitted to the hospital a catheter was inserted into the fistulous tract and 35 c.c. of 70 per cent diodrast were introduced. The visualizing cholangiogram not only outlined the dilated cystic duct but also revealed an impacted stone in the ampulla of Vater (Fig. 7). It was interesting to note how the cystic duct descended along the lateral side of the common hepatic duct, the two fusing behind the duodenum to form a short choledochus.

Fig. 7.—The external biliary fistula was injected with 70 per cent diodrast. The cystic duct is so dilated that it resembles a reformed gall bladder. Observe how the cystic duct descends along the lateral margin of the common hepatic bile duct. The common bile duct is obstructed by an overlooked stone.

Apparently the unusual position of the cystic duct caused the first operator to leave the major portion of it behind. The choledochal stone so obstructed the flow of bile that the increased hydrostatic pressure caused the cystic duct to dilate until it resembled a small gall bladder. A cure was effected by excising the fistulous tract and the cystic duct and extracting the impacted stone from the ampulla of Vater. After the common hepatic bile duct was drained for fourteen days, operative cholangiograms demonstrated that the pancreatitis had subsided, therefore all tubes were removed. He has remained well.

CYSTIC DUCT STONES

One is annoyed by the frequency with which the stump of the cystic duct harbors elusive calculi which cannot be detected by palpation. The tortuosity

of the duct and the presence of the spiral valves of Heister preclude informative probing, causing the unmolested stones to be left behind to incite undesirable symptoms.

CASE 4.—A saleswoman, 58 years of age, had had the gall bladder removed two years prior to the present hospital admission. Since that time she had never been free from gaseous distention, epigastric pain, and jaundice. A second laparotomy revealed an enlarged common bile duct, a dilated and indurated stump of the cystic duct, and diffuse induration of the pancreas. An operative cholangiogram was obtained by injecting 20 c.c. of 70 per cent diodrast directly into the dilated choledochus (Fig. 8). There were dilatation of the entire biliary tree, enlargement of the cystic duct, and obstruction of the ampulla of Vater by a swollen edematous pancreas. So effective was the choledochal obstruction that there was a reflux of

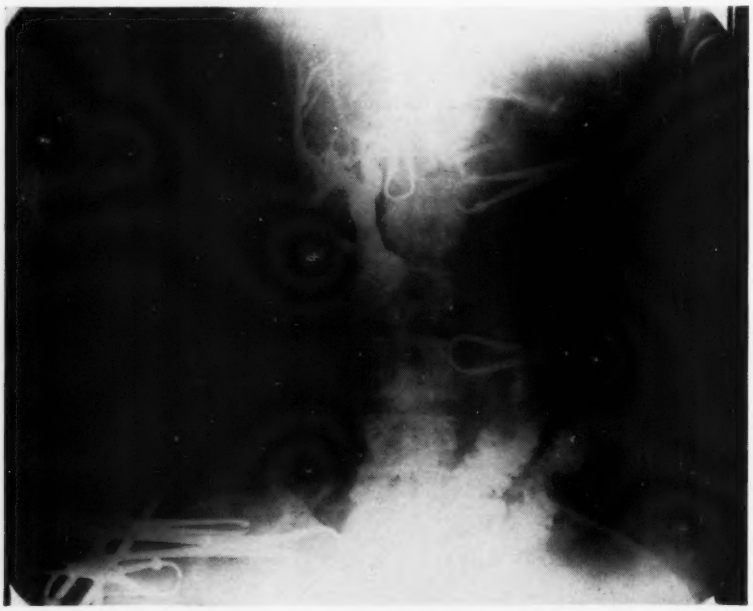

Fig. 8.—The operative cholangiogram reveals a dilated stump of the cystic duct. The head of the pancreas is so swollen that it is producing a partial obstruction of the ampulla of Vater. Some of the diodrast, however, has escaped into the jejunum. A laparotomy disclosed the dilated cystic duct to contain a small stone. The irritation from the cystic duct calculus apparently initiated a spasm of the sphincter of Oddi which caused a reflux of the irritating biliary secretions into the pancreatic ducts.

diodrast along the duct of Wirsung. The cystic duct was excised and found to contain a small calculus. The choledochus was opened and explored but no stones could be found. Apparently the cystic duct stone had produced a spastic contraction of the sphincter of Oddi, causing a reflux of the irritating bile along the pancreatic ducts, thus producing an acute pancreatitis. She made an excellent recovery and has been free of symptoms since the operation.

CASE 5.—A woman, 50 years of age, had complained of recurring attacks of colic and jaundice. Two years prior to the present hospital admission a gall bladder containing many small stones had been removed. She was well for two months then she experienced a return of both pain and jaundice. At the second exploration a dilated stump of the cystic duct was found containing a dumbbell-shaped calculus. One end of the stone protruded into the common hepatic bile duct to produce a complete biliary obstruction (Fig. 9). Further exploration demonstrated the presence of three stones in the common hepatic duct. Excision of the cystic duct and removal of the offending calculi alleviated all symptoms.

Fig. 9.—The stump of the cystic duct contains a dumbbell-like stone which protrudes into and obstructs the common hepatic bile duct. Observe the three small stones lodged above the cystic duct calculus.

Fig. 10.—The external biliary fistula was injected with 70 per cent diodrast, thus visualizing redundant cystic duct and choledochal stone. It is interesting to note the kinking obstruction of the common hepatic bile duct caused by the traction of the cystic duct.

TRACTION KINKING OF THE COMMON HEPATIC BILE DUCT

A long residual cystic duct presents another hazard by exerting undue traction on the main bile ducts thereby effecting an obstruction. Not infrequently the free end of the cystic duct becomes firmly attached to the ventral surface of the liver, to the duodenum, or to the colon. As cicatricial shortening takes place the traction becomes more intense and so distorts the contour of the common hepatic bile duct that a kinking obstruction may ensue.

CASE 6.—A woman, 43 years of age, had had the gall bladder removed three months previously. She had been annoyed by the persistent drainage of bile from a biliary sinus. During the past month she had complained of recurring paroxysms of biliary colic. In order to visualize the biliary radicals the external fistula was injected with 70 per cent diodrast and an x-ray view was taken (Fig. 10). The long cystic duct had produced a traction kinking of the common hepatic bile duct and the ampulla of Vater was obstructed by an impacted stone. At the second operation the dilated common hepatic duct was so distorted by the lateral traction of the cystic duct that it formed an acute angle with he choledochus. The ampullary stone did not effectively block the choledochus as perfusion solutions readily entered the duodenum. The choledochal stone was removed, the cystic duct was excised, and the common hepatic duct was freed from its cicatricial bed, thereby replacing it in proper alignment. She made a most pleasing recovery.

Fig. 11.—Drawing representing a kinking obstruction of the common hepatic bile duct caused by the persistent traction of the stump of the cystic duct as it had become attached to the ventral surface of the right lobe of the liver.

CASE 7.—A man, 56 years of age, had had a cholecystectomy five years previously. He was well for two years then stated that "my gall bladder trouble returned." During the past year he had several attacks of painless jaundice. A second laparotomy disclosed a fibrotic stump of the cystic duct attached to the ventral surface of the right lobe of the liver (Fig. 11). It was exerting so much traction of the lower end of the common hepatic duct that an ob-

structive angulation resulted. The hepatic ducts were all dilated to about three times normal size. The choledochus was very small, collapsed, but patent. Perfusion fluids injected into the common bile duct readily entered the duodenum. The fibrotic cystic duct was excised, thus permitting the common hepatic duct to assume its normal position. This restored the normal continuity of the large bile ducts, for when 70 per cent diodrast was introduced into the upper end of the common hepatic duct it immediately flowed into the choledochus and then escaped into the intestinal tract. The patient has since enjoyed the best of health.

DISCUSSION

It is self-evident that a continuation of gall bladder distress following a cholecystectomy can be attributed to three fundamental causes—incorrect preoperative diagnosis, residual hepatic disease, and incomplete surgery. The clinician must eliminate such confusing diseases as primary hepatitis, hepatic cirrhoses, peptic ulcers, appendicitis, gastrointestinal allergies, and carcinomatous lesions of abdominal viscera. Likewise, one cannot expect a cholecystectomy to restore hepatic functions to a normal level if they have been disturbed by a long-standing biliary stasis, cholangitis, or cirrhosis. Only an early diagnosis combined with prompt surgical intervention can prevent these late sequelae. The surgeon, however, must recognize the fact that he has often failed to remove the provocative focus responsible for initiating the biliary dysfunctions. The frequency with which secondary operations must be performed on the biliary tract justifies this conclusion.

How can the surgeon minimize this mistakes? The answer to this question has several components. First, experience dictates that no physician should elect to operate on the gall bladder unless his training and familiarity with the biliary system will permit him to explore the large bile ducts and correct complicated intraductal problems. Unfortunately, there are no preoperative guides, clinical symptoms, physical signs, or laboratory tests which can be used to segregate those cases which have intraductal pathology from the uncomplicated cases. This must be done during the operation.

Second, it is essential that the entire gall bladder and its cystic duct be removed whenever a cholecystectomy is being performed. Adequate exposure, complete muscular relaxation, and careful dissection permit one to expose the cystic duct at its juncture with the common hepatic bile duct so that it can be ligated without injury to the latter. It might be argued that attempts to excise the cystic duct completely will result in traumatism to the large bile ducts. This need not happen if the cystic duct is completely exposed. Operators incapable of performing complete anatomic dissections of the cystic duct should not elect to remove the gall bladder. We have presented cases which demonstrate the manner in which a diseased residual cystic duct can and does produce biliary dysfunctions following a cholecystectomy. In our series of twenty-nine patients requiring secondary operations on the biliary system, there were twenty-seven instances in which the primary operations were performed by occasional operators whose fear of injuring the choledochus compelled them to assume what they felt to be safe surgery. Their patients, however, had to have a second operation to remove the diseased cystic duct, which should have been taken care of during the first exploration.

Third, we feel it is the obligation of every surgeon to determine the functional integrity of the choledochus and the common hepatic bile ducts before closing the abdomen. Failure to palpate the intraductal stones affords no assurance that they are not present. Even surgical exploration may fail to locate these elusive calculi. Fortunately, errors of omission can be minimized greatly by exploration of the entire biliary system roentgenographically while the patient is still on the operating table. Pathologic abnormalities are detected easily and corrective operations can then be employed. This tends to minimize the need for repetitious operations. The technique of cholangiography is simple and has been described in previous publications. Walters and Thiesen,[8] Macdonald,[6] Best and Hicken,[1] Mirizzi,[7] and Hicken and co-workers[3, 4, 5] have utilized such studies for a number of years.

SUMMARY

Annoying biliary dysfunctions, which persist after cholecystectomy, are often caused by an irritative focus located in the residual stump of the cystic duct. Representative cases of reformed gall bladders, stones in the stump of the cystic duct, persistent external biliary fistulas, and traction kinking of the larger bile ducts are presented to demonstrate how the diseased cystic duct can and does produce these undesirable sequelae.

It is surprising to see how frequently the surgeon fails to remove the diseased cystic duct thus permitting the pathologic process to spread to the larger bile ducts. Certain anatomic abnormalities of the cystic duct, such as variations in its length, configuration, and relationship to the common hepatic bile duct, account for its incomplete removal. Operative cholangiograms accurately visualize existing ductal abnormalities thereby permitting the surgeon to excise the entire cystic duct.

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CAUSALGIA

A Review of Its Characteristics, Diagnosis, and Treatment

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DEFINITION AND INTRODUCTION

IT IS the purpose of this paper to review an experience with fifty-two patients suffering from causalgia. In such a study of causalgia, it is imperative that one establish criteria upon which the diagnosis can be made. As remarked by Pollock and Davis,[1] "there is some confusion as to what constitutes a case of causalgia." The original description of the syndrome, by Mitchell, Morehouse, and Keen,[2] is quite specific, and we feel should be followed more strictly. In accordance with this original description, and with the data gathered from our studies, we have formulated a rather strict definition of this condition, which has been employed in our consideration of these cases.

We consider causalgia to be a clinical syndrome associated with a lesion of a peripheral nerve containing sensory fibers, manifested by pain in the affected extremity; this pain is usually of a burning character and is usually located in an area corresponding in general to the cutaneous distribution of the involved nerve. An integral characteristic of this pain, one whose presence is necessary in order to make the diagnosis, is its accentuation by certain disturbing features in the affected individual's environment. There are other aspects of this pain to be discussed more fully later, but the foregoing seems to be a workable definition.

It is obvious that such a definition is a purely arbitrary one, and it is a definition with which many might disagree. We freely admit that there are other painful states associated with injuries to peripheral nerves which some might include under the term causalgia. Some of these other painful states have been referred to as "minor causalgia" by Homans,[3] and as "reflex dystrophies of the extremity"[4] and as "causalgic states"[5] by de Takats, to mention only a few of the many descriptive terms which have been employed. Albeit true that these and other conditions, such as phantom-limb pain, may have the same pathogenesis as causalgia, it seems confusing to employ the term causalgia in reference to them. We arbitrarily have excluded from our group all such cases which do not meet entirely our criteria for the diagnosis of true causalgia. It would probably be preferable to employ a more general term, such as post-traumatic pain syndrome, for these latter cases. We feel that for purposes of accuracy as well as clarification it is preferable to use the term causalgia only in a sharply defined sense.

The term causalgia was first used by Mitchell, Morehouse, and Keen[2] in 1864 in a monograph presenting their experiences with peripheral nerve lesions

Received for publication, April 8, 1946.

encountered during the Civil War. According to Pollock and Davis,[1] however, as early as 1813 Alexander Denmark had given an accurate description of a clinical condition which was undoubtedly the same as that which was later called causalgia. Since the introduction of the term in 1864, the syndrome has been the subject of articles appearing sporadically in the literature. The enormous volume of peripheral nerve injuries coincident with World War II has provided the material for numerous reports both in this country and abroad. Among these are articles by Spiegel and Milowsky,[6] and Mayfield and Devine.[7] Due to the infrequency with which peripheral nerve injuries are encountered by any one individual in civilian practice, causalgia has in the past not been familiar to the average practitioner of medicine. This is unfortunate, for it is a condition which, when recognized, responds in a gratifying manner to proper therapy. Moreover, once a physician has encountered this condition, he is not likely to forget the haggard, sleepless, pain-racked patient with the causalgic extremity.

The group of patients comprising this study were observed in a series of approximately 2,850 patients with peripheral nerve injuries, who had a total of 3,276 major nerve lesions,* admitted to the Neurosurgical section in an Army General Hospital in the Zone of the Interior in World War II. This study was aimed at the elucidation of several aspects of the problem, namely, (1) the pathogenesis of the condition, (2) the morphologic lesions found in the involved nerves, (3) the differentiation between causalgia and other post-traumatic painful states in the extremities, (4) the treatment of causalgia, and finally, (5) the factors influencing the results obtained by sympathectomy. No claim is made that anything of positive value has been added to the fundamental understanding of this complex clinical problem. Yet it is believed that such a mass of data upon a relatively uncommon condition and the conclusions derived therefrom are worth recording.

MATERIAL AND SOURCE OF DATA

It would have been ideal had we been able to include in this report all cases of peripheral nerve injuries with pain in the involved extremity. Unfortunately, this was not possible because many of the patients who passed through this neurosurgical center had been discharged and their charts were not available. Thus, there have been undoubtedly on our service many cases of mild or perhaps moderate causalgia which are not included in this report. There are probably many other cases of less specific post-traumatic pain which have also been omitted.

We have data, however, on every patient with causalgia or post-traumatic pain of a more indefinite nature, who has been subjected to dorsal or lumbar sympathectomy in this hospital. We also have data on a small number of patients with causalgia who for one reason or another were not subjected to sympathectomy. These data comprise the basis for this paper.

This series totals sixty-one cases. In forty-nine of these cases the patients were carefully interviewed by us personally, and a complete analysis of their pain, of their nerve injury, and of their response to treatment was possible. We

*Nerve lesions in the hand were excluded. Brachial plexus injuries were classified as a single nerve lesion.

feel that the data on this group are complete. Most of the material which we shall present is based on this group of forty-nine completely evaluated cases. In addition, there were twelve charts available to us, although the patients themselves had been discharged and could not be interviewed. We have found that even though the progress notes were complete, these charts did not give us sufficient information to allow a complete analysis. Arbitrarily then we decided to use this group of twelve only in evaluating the gross end results of treatment. All other data are based on the group of forty-nine cases alone (Table I).

TABLE I. OVER-ALL DATA

Total number of cases	61		
Personally interviewed		49	
Data from records		12	
Total Group	61		
Causalgia		52	
Upper extremity			32
Lower extremity			20
Atypical		9	
Upper extremity			5
Lower extremity			4
Personally Interviewed	49		
Causalgia		40	
Upper extremity			22
Lower extremity			18
Atypical		9	
Upper extremity			5
Lower extremity			4
Treatment of Causalgia			
Sympathectomy	48		
Dorsal		33	
Lumbar		15	
Resection of nerve lesion	5*		

*One patient was subjected to both sympathectomy and resection of the nerve lesion.

PATHOGENESIS

Despite the fact that causalgia has been an established clinical entity for a long period of time, and in spite of the widespread attention that the entity has received from numerous investigators, it has remained an inadequately explained syndrome, because of the failure of anyone to provide concrete evidence as to the true physiopathologic nature of the condition. Numerous attempts have been made to explain the pathogenesis of causalgia, but it is to be emphasized that thus far no conclusive explanation has been presented.

Mitchell, Morehouse, and Keen[2] attributed the syndrome to an ascending neuritis affecting the damaged peripheral nerve. Other observers have assigned as the cause of the pain a "neuritis of the periarterial sympathetics," or an "inflammation of the sympathetic fibers in the nerve trunks."[1] It has been stated by some authors that an abnormal vasomotor activity is a causative factor in causalgia. De Takats and his co-workers have, in the past few years, written extensively upon this aspect of causalgia.[4, 8-10] These authors take the view that the syndrome is a vasomotor reflex disorder based, in all probability, upon the axon reflex. De Takats believes that the excitation of efferent vasodilators through the axon reflex produces a humoral substance (probably histamine) at the end organs, which is responsible for both vasodilatation and pain. However,

it should be noted that among the group of cases upon which de Takats bases his conclusions is a wide variety of anatomic lesions and clinical states. Many of these cases, we believe, do not represent true causalgia.

The sympathetic nervous system does seem in some way involved in this condition, as is suggested by many recent observers, although the evidence that this is true is not complete. If it is true, it yet remains to be demonstrated in what manner the sympathetic nervous system is involved. Two possibilities exist: either it plays some role in the production of the pain or it merely serves as the pathway for conduction of the pain. The information at present available does not allow a definite conclusion in this regard.

It can only be admitted that much yet remains to be disclosed in the pathogenesis of causalgia. The facts will come to light only as our knowledge of fundamental physiology and anatomy, including that of the nervous system, is increased.

ANATOMIC NERVE LESION

The anatomic lesions in the involved nerves were investigated in all instances possible. Many of the nerves injured in our patients were not explored because they showed spontaneous recovery of function. However, in a little less than one-half of our cases, the involved nerve was explored surgically. Without going into extensive detail, suffice it to say that a great variety of lesions were found in these nerves, none of which differed in any specific regard from the lesions found in a large group of peripheral nerve explorations on patients without causalgia. On gross inspection the appearance of nerves in the causalgic group varied widely. In some nerves there was no demonstrable evidence of damage; in others the lesion appeared to be composed of neuroma and glioma connected only by scar tissue. There were all gradations of lesions between these two extremes, and there was no correlation between the severity of the causalgic pain and the anatomic lesion found.

Obviously the nerves which were without surgical indication for resection were left in situ. However, those showing severe damage with neuroma and glioma formation were on five occasions resected and end-to-end anastomosis was done because of the anatomic lesion found at operation. The nerve ends resected in this small group of cases were studied microscopically.* The microscopic appearance of these nerves was compared with that of the nerve ends which had been resected in a large number of patients not showing causalgia. No abnormality was found in the causalgic nerves which distinguished them from the specimens resected in patients not suffering from causalgia.

Further, in each of these five cases, silver stains were made of the distal ends and where possible of the fibrous bridge between the neuroma and glioma. In three of these five cases, at operation one or two funiculi (comprising one-sixth to one-eighth of the nerve trunk) were seen on inspection to traverse through the site of injury. For technical reasons, a partial neurorrhaphy was

*This study was carried out by Major G. D. Ayer, Jr., Chief of the Laboratory Service, O'Reilly General Hospital.

decided against and a total resection was performed. In these three instances, silver stains showed variable numbers of small axons in the distal ends. Examination of the bridge between the neuroma and glioma showed naked funiculi crossing this area. In the other two cases, the neuroma and glioma appeared grossly to be in continuity only by cicatrix. In one in which the bridge could be examined microscopically a few naked fibers were seen crossing it, and some small axons were seen in the cross section of the distal end. In the other, only the distal end could be examined, and this showed many scattered tiny axons.

Considerable care must be exercised in the interpretation of these data. In the three cases in which a few funiculi seemed, on gross examination, to cross the level of injury, it is reasonable to believe that the anatomic lesions were never complete. The other two cases are not so clear, however. There are three possible explanations of the microscopic findings in them. The first is that a few fibers were spared at the time of injury and remained in continuity. The second is that the lesion in these instances was complete at the time of injury, and that subsequently naked fibers grew out from the proximal stump across the cicatrix to enter the distal glioma. The third is that the axons seen in the distal end represent those growing in retrograde fashion from axis cylinders entering the nerve distal to the level of injury. This situation has been found to exist in another instance.[11] Obviously, if the second explanation is the correct one, the causalgia (whose onset in these two instances was immediate) did exist for a time in the presence of a complete nerve lesion. If the third is true, again the syndrome has existed in the presence of a lesion which is locally complete. It is unfortunate that microscopically it is impossible to distinguish among these three possibilities. Thus, we do not know whether the lesion was or was not complete at one time in these two cases. The data indicate, however, that it is not yet conclusively demonstrated that causalgia exists *only* in incomplete anatomic lesions.

In summary then, the only contribution which our data make is that they lay open to question the contention that causalgia occurs only in anatomically incomplete lesions. Our data do emphasize that the lesions may vary tremendously, and that occasionally only a few scattered axons can be found in cross sections and longitudinal sections of the distal end of a nerve which on gross examination appears to have been completely divided.

CLINICAL CHARACTERISTICS OF CAUSALGIA

In the majority of cases the causalgic pain began either immediately upon wounding or within a few hours thereafter. Of course, many of the patients were mentally dulled either by the wound or by the sedation at the time of injury, and did not appreciate the pain until eight to twelve hours following injury. For all practical purposes, however, in these men we may consider the pain to have begun immediately. However, in about 20 per cent of the group of forty carefully considered cases of causalgia, the pain began anywhere from three days to four weeks following wounding. In all cases save one, the pain was as severe at the beginning as it ever became, not increasing in severity once it started. In one individual, however, the pain began about seven days

following wounding, became progressively worse during the ensuing two or three weeks, and then remained at constant intensity after that period.

In each patient of this group, except one, the pain was unremitting once it began. Many of the patients noticed variations in the intensity of the pain from time to time, but all save this one stated that at no time after the onset were they completely free of pain. In one individual who meets definitely the causalgia criteria as outlined earlier in this paper, the pain was not constant. In this patient the pain was never present at night and was never present during rainy weather. Other than these times he always had pain.

The type of pain which these patients suffer has been recorded on many previous occasions. It will add little for us to review the literature in this respect, but rather we shall review the types of pain manifested. The description of the pain has been obtained from the patients by personal questioning, care being taken not to prompt them and not to place descriptive words before them. It is important to realize, of course, that the same pain may be variously described by different individuals, due to varying past experiences and varying commands of language. Taking these factors into account, it can still be stated that the type of pain in causalgia does seem to vary somewhat from individual to individual.

It is obvious from Table II that burning is the word most frequently used by patients to describe the pain of causalgia. Sometimes this word is used alone and on other occasions other words such as throbbing, aching, or twisting are used to qualify it. In three instances, however, the patients noted no burning whatsoever, and in eleven instances burning, although present, was a minor feature of the complaint. Throbbing was used with fair frequency to describe the discomfort, although in no instance in either the upper or lower extremity was the pain described as exclusively throbbing. Aching was a prominent feature of the causalgia in a few cases. Three men with upper extremity causalgia described the pain chiefly as one of "pressure, as if someone were wringing the blood out into the ends of the fingers and as if the finger tips were about to burst." Knifelike, stabbing pains and twisting, crushing pains were bitterly complained of by a few of the patients.

It has been stated that the distribution of the pain in causalgia corresponds in general to the cutaneous distribution of the involved nerve. In both the upper and lower extremities approximately 60 per cent of the patients had pain limited strictly to the distribution of the involved nerve. However, roughly 40 per cent had pain in the hand or in the foot *not* strictly limited to the cutaneous distribution of any one nerve. It is of interest to note that in the group with strict anatomic distribution of the pain, roughly 70 per cent had accompanying complete sensory lesions of a second major nerve in the involved extremity, while in the group with generalized pain only 15 per cent had such accompanying complete sensory lesions. It is possible, then, that the reason for the pain's being strictly localized in certain cases is that an anesthetic area in the affected hand or foot prevents appreciation of pain in areas other than that supplied by the causalgic nerve. On the other hand, in patients with

TABLE II. THE PAIN OF CAUSALGIA

TYPE OF PAIN	UPPER EXTREMITY (% OF TOTAL GROUP)		LOWER EXTREMITY (% OF TOTAL GROUP)	
Burning				
With burning	90		87	
All or mainly burning		57		67
Some burning		33		20
Without burning	10		13	
Throbbing				
With throbbing	48		13	
All or mainly throbbing		14		0
Some throbbing		34		13
Without throbbing	52		87	
Aching				
With aching	24		27	
All or mainly aching		9		13
Some aching		15		14
Without aching	76		73	
"Pressure"				
With "pressure"	14		0	
All or mainly "pressure"		14		
Some "pressure"		0		
Without "pressure"	*		*	
Knifelike, Stabbing				
With knifelike stabbing	10		34	
All or mainly knifelike stabbing		5		34
Some knifelike stabbing		5		0
Without knifelike stabbing	*		*	
Twisting, Crushing				
With twisting, crushing	14		20	
All or mainly twisting, crushing		5		7
Some twisting, crushing		9		13
Without twisting, crushing	*		*	

*Not calculated.

generalized pain the lack of any anesthetic area may allow an overflow of the painful sensation to other parts of the extremity.

Another characteristic of causalgia is that in most cases the lesion in the involved nerve is clinically incomplete. Thus, in 72 per cent of the forty patients personally interviewed the paralysis of the involved nerve as indicated by clinical examination of the patient was definitely incomplete. In the remaining 28 per cent the individuals when first seen with causalgia manifested complete motor and sensory paralysis of the involved nerve. A few of these patients spontaneously recovered function at a later date, but the remainder were explored. In some a minimal lesion was found at operation requiring either a neurolysis or no operative treatment. As noted previously, in five instances it was deemed necessary to carry out a resection and neurorrhaphy.

As has been pointed out, causalgia is associated with a lesion of a peripheral nerve containing sensory fibers. In our experience lesions of mixed nerves have most commonly been associated with the syndrome although occasionally injury to a purely sensory nerve may produce the syndrome. Injury to the median nerve in our group of cases was the most common lesion responsible for the production of causalgia. Injury to the sciatic nerve which involved the tibial component alone was slightly less common. The frequency with which

TABLE III. NERVES INVOLVED IN TOTAL CAUSALGIA GROUP

Upper extremity	32	
Brachial plexus		3
Median		28
Radial		1
Lower extremity	20	
Sciatic (posterior tibial component)		14
Sciatic (peroneal component)		3
Saphenous		3

TABLE IV. LOCATION OF WOUND

Upper extremity	32	
Axilla		9
Upper arm		16
Elbow and forearm		7
Lower extremity	20	
Buttocks		7
Thigh		13
Lower leg		0

other nerves are involved is indicated in Table III.* The location of the wounds in this group is indicated in Table IV.

AGGRAVATIONS AND RELIEFS OF PAIN

A characteristic feature of the pain of causalgia is its aggravation by certain disturbing things which happen around or to the patient. It is our conclusion after examination of the data which we have gathered that this is probably the single most constant feature of the group which we have set aside as true causalgia. By virtue of the very definition which we have adopted, 100 per cent of the patients who we believe suffer from causalgia manifest this tendency to aggravation. Those without it, we have not considered to have causalgia. The precise factors which aggravate the pain vary from individual to individual.

In Table V is indicated in general the type of factors which aggravated the pain in these patients. This table is not broken down into the upper and lower extremities, for there is no significant variation in this respect between the two groups. The patients with lower extremity causalgia, however, tend

TABLE V. AGGRAVATING FACTORS

FACTOR	PER CENT OF CASES AGGRAVATED
Moving or touching involved part	74
Sudden jar	61
Loud noise	58
Emotional excitement	47
Touching slick objects such as bed sheets or paper	28
Touching patient with a dry finger, but not with a wet finger	19
Looking up in the air or at high objects	17
Touching the patient's body at any point	14
The sound of certain words, such as paper or slick	8

*Since this article was written a patient has been encountered who had an incomplete lesion of the cervical plexus with severe causalgia in the occipital and postauricular regions of the scalp. He has been completely relieved by dorsal sympathectomy of the type to be described later.

to be somewhat less affected by these factors than are those with upper extremity causalgia. This aspect of the syndrome is a striking one. Dramatic examples are the few individuals in whom the mere sound of the spoken words slick or paper provoked severe exacerbation of the pain. One patient could not tolerate the sound of papers rattling in the bed next to his because of the intense aggravation of the causalgic pain. Another patient had pain more severe than usual during the voyage back from overseas, because the water looked so smooth to him as he gazed upon it. Still another unfortunate victim of this condition developed a tremendous fear of flies, because he was constantly apprehensive lest they alight upon his body and aggravate the constant burning pain in the hand. One of these men could not even look at a picture of a high building without marked increase of pain. These patients not infrequently go to extremes in order to avoid any noise or disturbing factor. In the more severe cases the patients have on occasions locked themselves in an isolated room, put their heads beneath the covers, and refused to talk with anyone who came near them. Of course, some are much less dramatic and merely shield the affected part to prevent one's touching it.

It is important at this point to differentiate the aggravation of causalgic pain produced by touching the affected part from hyperesthesia. Hyperesthesia, in peripheral nerve injuries, is occasionally very pronounced and thus disabling; it is, of course, produced by touching the affected part. This is not causalgia, however, and the failure to distinguish it clearly from causalgia is apparent in much of the recent literature. Furthermore, hyperesthesia is not a necessary concomitant of causalgia, although occasionally they do coexist. In patients afflicted with hyperesthesia, the pain is not constant, is not usually burning in character, and is not aggravated, or in point of fact, produced, by anything except contact with the hyperesthetic part. This distinction is an important, although occasionally difficult, one to make.

Many of the patients with causalgia discovered that certain things would alleviate the pain. The vast majority of them noted that the pain was somewhat alleviated by very quiet surroundings without any disturbing features. Roughly 50 per cent of the men found that wrapping the affected part in a wet cloth was helpful. Most of the men preferred a wet cool cloth rather than a wet warm one, but some did prefer the latter. In a few severe cases of upper extremity causalgia the patients even filled their shoes with water during the day and slept with wet socks on their feet at night because it tended to relieve the pain in the extremity. This, of course, was noted by Mitchell and his collaborators in their original description[2] of the syndrome. Several found that sleeping on smooth sheets and pillow cases was intolerable and requested rough towels or blankets instead. Our data do not indicate that these alleviating factors, which many of the men found, are a really integral feature of the causalgic syndrome. As stated, 50 per cent of the men with otherwise typical causalgia did not find that wrapping the affected extremity in wet cloths or sleeping on rough rather than smooth bedclothes was beneficial.

About 60 per cent of the men with causalgia noted a difference in the pain during the day as contrasted with the night. Of this group about two-thirds

found the discomfort to be partially relieved by nightfall, while about one-third found the pain to become worse at night. It is also interesting to note that some patients found that the pain was worse in hot weather, others in cold weather, while some noted no relation between pain and the temperatures of their environment. There was no correlation whatsoever between the aggravation of the pain by heat or by cold and the preference of hot or cold wet rags on the extremity for the relief of pain. It is apparent from our data that although such things as the time of day and the temperature of the environment do affect the pain in some cases, this is not a constantly aggravating factor such as noise, excitement, sudden jars, and the like.

A CONSIDERATION OF ATYPICAL POST-TRAUMATIC PAIN

Having presented the features characterizing true causalgia, we shall now consider briefly other painful post-traumatic states. Such syndromes have been designated by various terms; a few examples are Sudeck's atrophy, post-traumatic angiospasm, minor causalgia, and reflex sympathetic dystrophy. De Takats and Miller[8] have grouped many of these together under the term "reflex dystrophy of the extremities." These authors describe reflex dystrophy as ". . . severe, persistent pain of a burning character with paroxysmal aggravations, presented by a patient whose injured limb is properly immobilized, noninfected, and seemingly on its way toward a normal course of recovery. . ." Injury to nerves, blood vessels, periarticular structures, and rarely to bone are said to give rise to such a disorder. Further, it has been stated that the condition may develop after a minor injury to an extremity not involving bone, nerve, or a major vessel. The early stages of such a syndrome are characterized[14] by hyperemia, while in the chronic stage, signs of excessive vasomotor activity dominate the picture, with cold, clammy skin and trophic changes in skin and muscles. It is possible that many of the immobile clawlike hands with hard, fibrotic forearm muscles described as classical cases of Volkmann's contracture may represent terminal stages of reflex dystrophy.

Despite the description of reflex dystrophy quoted from de Takats and Miller, most of the cases they reported do not quite fit this description. If they did, then they should probably be considered to be true causalgia. Further, none of the cases quoted in recent literature[3, 4, 5, 8-10, 12, 13] on this ill-defined group involved constant pain, usually of a burning character, invariably aggravated by disturbing factors in the patients' environment and associated with injury to a peripheral nerve. For this reason, it seems advantageous not to employ the terms causalgia or causalgic to this group at all, but to limit the use of these words to the clearly defined group of cases originally referred to by Mitchell, Morehouse, and Keen. True, causalgia may be related to these other post-traumatic pain syndromes, but it is a clinical entity with sufficient diagnostic criteria to be separated from these other states. Such a sharp differentiation will clarify and simplify, rather than confuse, this entire subject.

We have had no experience with cases entirely similar to those quoted in the articles just mentioned. Furthermore, we have had no experience with post-traumatic pain syndromes in individuals suffering merely vascular, bone,

or soft tissue damage without peripheral nerve damage. As noted previously, such cases have been reported in detail by others. However, we will present in brief a small group of cases of atypical post-traumatic pain, occurring in individuals who have suffered peripheral nerve lesions. Cases such as these must be distinguished from true causalgia.

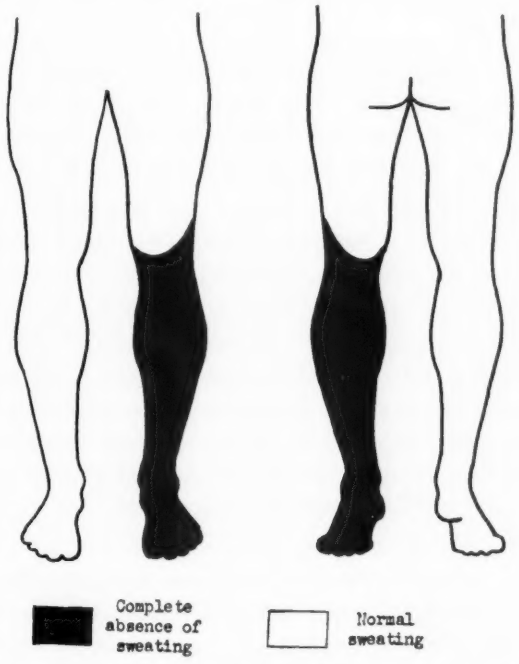

Fig. 1.—No relief of atypical pain following complete (Grade I) lumbar sympathectomy.

In one, the patient had a moderately severe, constant burning pain in the foot following a wound of the popliteal fossa. The pain began immediately after wounding and was constant, but was not aggravated by any of the factors aggravating causalgia. The presence of complete paralysis of the tibial and peroneal nerves caused us to explore these, and the anatomic findings demanded end-to-end anastomosis of both. There was no improvement in the pain. The second and third lumbar sympathetic ganglia were then removed extraperitoneally through a high transverse abdominal incision; postoperative dermometer readings showed the patient to be completely denervated from the area of the knee distally (Fig. 1). The pain was not improved in the slightest. After six weeks, a resection of the tibial suture line was carried out because of the poor appearance, microscopically, of the nerve ends previously resected; through the same incision a periarterial sympathectomy was performed on the femoral artery at the level of its emergence from the adductor canal. Following these procedures, and continuing to the present time, the patient has been relieved of the constant burning pain. Because of the complete lack of aggravation of the burning pain by noise, excitement, touching the foot, and the like, we do not consider this to be true causalgia.

Three patients were encountered in this group whose chief complaint was that they developed severe pain in the hand of the injured arm while in the cold. These men had varying degrees of minor pain constantly, not aggravated by the factors aggravating causalgia. Dorsal sympathectomy was performed, and following this procedure the men had complete relief of pain when in the cold. Their hands still became abnormally cold in the cool weather, but they were no longer painful.

An atypical post-traumatic pain syndrome was encountered in an individual suffering a simple dislocation of the left shoulder and an incomplete paralysis of the brachial plexus. He had the immediate onset of severe burning, aching pain in the hand. It was not aggravated by any known factor. Because procaine block of the stellate ganglion on three occasions gave complete relief of pain lasting three to thirty minutes, a dorsal sympathectomy was performed. Postoperative dermometer readings indicated that the sympathectomy was complete. Nonetheless the patient felt that, although he no longer had burning, the over-all discomfort was still so great that he was not significantly improved. Further study revealed a herniated nucleus pulposus in the cervical region, between the fifth and sixth cervical vertebrae on the left side. This was removed surgically, and following this he has shown gradual improvement and is now free of pain. It is our feeling that the pain in this patient was actually the pain of a cervical herniated nucleus pulposus, and was not causalgia, despite its burning, aching character.

In this atypical group of cases, there were three instances of pain in the lower extremity following minor peripheral nerve injury. These individuals had a sharp, stabbing, or aching pain in the foot, inconstant, and aggravated only by walking. Although we did not consider these causalgia, they were subjected to lumbar sympathectomy because they had shown a favorable temporary response to procaine block of the lumbar sympathetic ganglia. Two of these patients showed some improvement following this procedure, and one showed no improvement.

One last case, and a very instructive one, is that of an individual suffering a wound in the upper arm (producing a mild, incomplete paralysis of the median nerve) and wounds of the tip of the thumb and little finger. The only signs of median nerve damage were weakness of the opponens pollicis muscle and hyperesthesia in the distribution of this nerve. However, the patient complained bitterly of pain—not constant pain, but pain "like electric shocks" when anything touched the thumb, index finger, or middle finger. There was no burning and nothing produced this pain except touching these areas. It was so severe that he constantly protected this hand. Because of the mistaken diagnosis of causalgia, a dorsal sympathectomy was performed, which completely failed to relieve the pain. An external neurolysis on the median nerve in the upper arm similarly failed. Finally, the digital nerves in the thumb and middle finger were sectioned, a drastic procedure but one demanded by the patient. This immediately relieved the hyperalgesia, replacing it of course with anesthesia. The nerves to the index finger were not sectioned, and the

patient has learned to tolerate the discomfort in this digit. This case actually was not causalgia, and should not have been confused with it. It represents, actually, a severe hyperesthesia.

In concluding a discussion of these difficult atypical cases, we wish to state that the exclusion of some of these from the causalgic group might be considered an error. However, we have so separated them because the clinical syndromes presented by these men do not meet the requirements we have established for making the diagnosis of causalgia. If further experience proves this wrong, the classification must, of course, be revised.

THE TREATMENT OF CAUSALGIA

Causalgia, especially cases of mild or moderate severity, may subside spontaneously within a period of a few months. We have no data, unfortunately, concerning the frequency of this. However, when the condition is moderately severe or severe, procaine block of the sympathetic supply to the involved extremity should be performed. Infrequently, a series of three or four blocks, twenty-four to forty-eight hours apart, will relieve the pain to such an extent that the patient can tolerate it satisfactorily and thus does not require operative intervention. However, in our experience we have found that the pain usually returns to the preinjection level after thirty to sixty minutes, even after two or three successive blocks. It is then useless to persist in this, and one must turn to other methods of treatment.

One method which has been attempted is external or internal neurolysis of the lesion in the involved nerve. It has been stated by some that neurolysis or partial resection of the neuroma may provide relief in some cases; however, this has not been the experience of most workers. In four of our cases, neurolysis of the involved nerve had been done prior to sympathectomy, with no relief of pain in any instance. In general, it seems safe to assert that an external or internal neurolysis cannot be expected to relieve the pain of true causalgia.

However, if, apart from the attendant causalgia, there is an indication for exploration of the peripheral nerve, we believe that the nerve should be explored prior to sympathectomy if the patient feels that he can tolerate the causalgia during the postoperative period, should it not be relieved. On infrequent occasions, as demonstrated in our series, a patient with causalgia may clinically manifest complete paralysis of the involved nerve, associated with a lesion in that nerve which requires resection and neurorrhaphy; in such cases, of course, neurorrhaphy is performed. It has been our experience that such a procedure is sometimes followed by relief of the existing causalgia. This will be discussed in detail later.

Another operative procedure that has received considerable attention in the past is periarterial sympathectomy. This consists of stripping the adventitial sheath of a major vessel to remove the perivascular plexuses of sympathetic nerves in that segment of the vessel. It was popularized by Leriche and other European surgeons in the 1920's, but has never received wide favor in this

country. There is no sound anatomic basis to support the procedure, for the vessels of the extremities have a segmental nerve supply, the sympathetic fibers emerging from the somatic nerves at intervals throughout their course in an extremity. Further, experimental and clinical investigation has revealed that there is no more than a transient increase in blood flow in a limb after periarterial stripping.[14] Yet the procedure has been reported as yielding successful results in some cases. We have had no experience with this procedure in true causalgia.

Unquestionably the method of treatment giving the best permanent results is central sympathectomy. As far as we are able to discover, this was first employed in the treatment of causalgia by Spurling[15] in 1930. Of course, both dorsal and lumbar sympathectomy had been used prior to that in the treatment of certain vasomotor disorders of the extremities. This method of treatment was the basis of our management of the cases comprising this series. The technique of the procedure employed need not be described in detail, although a brief statement on the subject is in order.

The technique that we have used for dorsal sympathectomy is a slight modification of that described by Smithwick.[16] It consists of sectioning the sympathetic trunk below the third ganglion and dividing the gray and white rami between the second and third ganglia and their respective intercostal nerves. The central stump of the sympathetic chain is then sutured into the intercostal muscles below the second rib. The chain is approached through an oblique or paravertebral incision centered over the third rib, with subperiosteal resection of the inner segment of that rib and the corresponding transverse process. The operation leaves the ganglia in place and maintains intact most of the postganglionic fibers to the arm. Furthermore, since the lowest cervical and first dorsal ganglia are not disturbed, a Horner's syndrome is not produced. The procedure resulted in most cases in denervation of the entire arm, and variable portions of the chest, face, and scalp (as indicated by dermometer readings).

In the case of the lower extremity, it has been our practice to resect the second and third lumbar ganglia, with the intervening sympathetic chain. This has resulted in complete denervation of the lower extremity on the side operated upon, below the level of the thigh. Since the fourth lumbar ganglion, and those ganglia distal to it, are left in situ, the postganglionic mechanism again is left intact. We have used the anterior muscle-splitting approach of Pearl[17] and the lumbar approach. It is our impression that the former provides easier access to, and better exposure of, the sympathetic chain than the latter, except in large individuals with thick trunks and heavy abdominal musculature. In three recent instances, a high transverse abdominal incision has been very satisfactorily employed in the extraperitoneal approach to the lumbar ganglia. It is carried from a point roughly 2 cm. above and lateral to the umbilicus directly laterally to the level of the anterior axillary line, usually crossing the lower portion of the eleventh rib. The external oblique muscle is cut transversely in the direction of the skin incision, and the remaining layers are split in the

direction of their fibers. Care is taken to aim the split in the internal oblique muscle at a point about three inches cephalad to the umbilicus. This incision seemed to provide a more direct access to the lumbar ganglia to be resected, particularly the second, and thus was perhaps an improvement over the oblique, completely muscle-splitting incision.

In the early part of our experience, it is probable that on some occasions the second lumbar ganglion, and even in a very few instances the third, were not resected, but rather the chain and a ganglion distal to these were removed. This seems an easy pitfall when the anterior oblique incision is used unless care is taken to avoid it. As will be shown later, dermometer readings bear out this probability. Later, great care was taken to resect with all possible certainty the second and third lumbar ganglia and their intervening chain.

Sympathectomy in either the dorsal or lumbar region is not a difficult procedure. There were no deaths in our series, and few have been reported in the literature. The only complication that has been encountered is pneumothorax, occasionally associated with dorsal sympathectomy, and this, when it occurred, has caused no serious postoperative morbidity. Except in patients who have had previous chest wounds, with thickening and adherence of the pleura, this complication should not occur if the proper care is exercised. Of course, either dorsal or lumbar sympathectomy is a major operative procedure and should not be undertaken without due consideration.

The cases were selected for sympathectomy on the basis of the clinical syndrome. In all instances procaine blocks of the sympathetic ganglia to the involved extremity were carried out preoperatively. In most cases the results from such blocks paralleled the results obtained by sympathectomy. However, in a few instances adequate sympathetic blocks failed to give relief of pain when sympathectomy itself did provide a satisfactory result; and in several individuals sympathectomy did not produce as complete relief as had been temporarily produced by procaine block. Thus, in our hands preoperative blocking of the sympathetic ganglia was of some aid in prognosticating the relief from sympathectomy but was not completely correlated with the results from this procedure. Therefore, it is our conclusion that procaine block is not necessary in making the diagnosis of causalgia, and is not needed in making the decision for or against sympathectomy. However, because of the few instances in which some permanent relief followed several procaine blocks, this procedure probably should be used preoperatively.

An analysis of the results of sympathectomy is presented in Table VI. This over-all analysis includes not only the personally interviewed patients, but

TABLE VI. RESULTS OF SYMPATHECTOMY FOR CAUSALGIA

	PER CENT OF TOTAL GROUP			
	UPPER EXTREMITY		LOWER EXTREMITY	
RESULTS OF SYMPATHECTOMY	PER CENT	NUMBER OF CASES	PER CENT	NUMBER OF CASES
Class I	40	13	33	5
Class II	33	11	27	4
Class III	27	9	33	5
Class IV	0	0	7	1
Total	100	33	100	15

rather the entire series. Class I is comprised of those patients completely relieved of pain by sympathectomy. Class II includes those patients who have an excellent result from sympathectomy with nearly complete relief of pain, but who present a little residual difficulty. Anyone with residual pain of any type, no matter how slight, is included in this group rather than in Class I. Class III includes those patients with definite improvement in the causalgia, but with moderate residual pain. All patients included in this group felt that the sympathectomy was clearly worth while. Class IV is the group of failures from sympathectomy. In this group the patient had either no relief or so little relief that the operation was not worth while.

To summarize, the results of sympathectomy in this condition have been very gratifying. Of forty-eight patients so treated, only one felt the operation was not definitely worth while. On the other hand, less than one-half of the patients had total, complete, relief of pain. It is interesting to note that in all instances following surgery, the factors which once aggravated the pain no longer did so.

We recognize and wish to emphasize that the low percentage of failures from sympathectomy might be directly attributed to the fact that we excluded from the group of true causalgias certain cases which do not meet the criteria which we set down in the beginning of this paper. These cases were discussed previously. It is apparent that these patients responded less well to sympathectomy than those who meet the criteria of true causalgia.

The data were analyzed in an attempt to discover any factors which might indicate preoperatively which patients with true causalgia will have the most complete relief of pain following sympathectomy. Several factors must be considered.

One might inquire first if the type of pain, that is whether it was mainly burning, or aching, or throbbing, influences the result from sympathectomy. A careful attempt to correlate the type of pain with the result of sympathectomy showed absolutely no relation between the two. Some men whose main pain was a "bursting pressurelike" feeling in the finger tips had complete relief from sympathectomy, while others with identical pain had less relief. The same is true of burning or throbbing. Thus, from the type of pain which a man has, one cannot accurately predict the result that will be obtained from sympathectomy. We then tried to correlate the result from sympathectomy with the interval elapsed from the time of wounding to the time of sympathectomy. This again was a total failure and we found no correlation between this interval and the result of operation.

We then analyzed carefully the data concerning aggravation of pain. In order to analyze these data, we graded the aggravation on the basis of I to IV, Grade I being slight aggravation and Grade IV being marked aggravation by anything in the patient's surroundings. Examination of the data in Table VII gives a slight suggestion that those with the more severe aggravations tend to be more completely relieved by sympathectomy than the others. However, the data do not permit any definite conclusion in this regard.

TABLE VII. RELATION OF RESULT OF SYMPATHECTOMY WITH DEGREE OF AGGRAVATIONS

RESULT FROM SYMPATHECTOMY	GRADE OF AGGRAVATION (PER CENT OF TOTAL IN EACH CLASS) GRADE I	GRADE II	GRADE III	GRADE IV	TOTAL
Class I					
Upper extremity	0	25	50	25	100
Lower extremity	20	60	0	20	100
Class II					
Upper extremity	23	11	33	33	100
Lower extremity	25	75	0	0	100
Class III					
Upper extremity	0	67	33	0	100
Lower extremity	17	50	33	0	100
Class IV					
Upper extremity	0	0	0	0	0
Lower extremity	100	0	0	0	100

An extremely important consideration is—have the sympathectomies been adequate in each case? In order to answer this question we have estimated the completeness of the sympathectomy by measurement of the sweating in the involved extremity following surgery. The dermometer,[18] an instrument measuring skin resistance, was employed for this.* In nearly all these cases we have preoperative as well as postoperative dermometer readings, so that we know the amount of desweating present prior to sympathectomy resulting from the nerve lesion itself. Of course, varying amounts of the head, neck, and chest, as well as the arm, are sympathectomized by the upper extremity procedure, but only the arm data are pertinent and thus are included. Occasionally, following lumbar sympathectomy a portion of the thigh is denervated. However, all observers agree that the removal of the second and third lumbar ganglia usually denervates only the knee area and the lower leg, not the thigh. The estimates of completeness of sympathectomy given here refer, in the case of the upper extremity, to the area of the shoulder and that distal to it; in the leg, they refer to the area of the knee and that distal to it. We have arbitrarily graded the amount of desweating, and thus the completeness of the sympathectomy, in the following manner:

Grade I, Complete desweating of the area.
Grade II, No areas of normal sweating, but a few very small scattered areas of slight sweating.
Grade III, Incomplete desweating with some areas of normal sweating.
Grade IV, No change in sweating from preoperative status.

Although one strives always for complete and total desweating, it has been our impression that these patients having Grade II desweating are satisfactorily sympathectomized. Grade III desweating, however, represents a definitely incomplete sympathectomy. In the upper extremity, only one patient tested was classed in Grade III, and this was one in whom the operator had difficulty in identifying the second thoracic sympathetic ganglion, and probably only the

*These measurements were very kindly made for us by First Lieutenant Ann Martin in the Physical Therapy Department, O'Reilly General Hospital. The Neurodermometer made by A. R. Spartana Co., Baltimore, was employed.

third was decentralized. However, the patient was completely cured of a severe causalgia. In the lumbar group, there were four instances of incomplete sympathectomy; as stated previously, probably the second lumbar ganglion, and perhaps the third, were not removed in these cases. The incompleteness in each instance showed itself as a varying area of normal sweating somewhere in the distribution of the saphenous nerve. One of these patients, operated upon recently and on whom this error should not have been made, showed no relief of pain following sympathectomy. Subsequent exploration of the tibial nerve in this patient disclosed a lesion which necessitated resection and neurorrhaphy; no relief in the pain was noted. This patient is still under observation. The other three operations, done earlier, had entirely satisfactory clinical results from the incomplete sympathectomy.

TABLE VIII. RELATION OF RESULT OF SYMPATHECTOMY WITH COMPLETENESS OF DESWEATING

	COMPLETENESS OF DESWEATING (PER CENT OF GROUP TESTED IN EACH CLASS)				
RESULT FROM SYMPATHECTOMY	GRADE I	GRADE II	GRADE III	GRADE IV	TOTAL
Class I					
Upper extremity	17	67	16	0	100
Lower extremity	50	0	50	0	100
Class II					
Upper extremity	0	100	0	0	100
Lower extremity	50	25	25	0	100
Class III					
Upper extremity	40	60	0	0	100
Lower extremity	0	100	0	0	100
Class IV					
Upper extremity	0	0	0	0	0
Lower extremity	0	0	100	0	100

Note: 1. In the upper extremity group the 16 per cent of Grade III desweating in the Class I results represents one case.

2. In the lower extremity group the 50 per cent of Grade III desweating in the Class I results, the 25 per cent in the Class II results, and the 100 per cent in the Class IV results, represent a total of four cases.

Unfortunately the entire series could not be tested, and the number of cases represented in Table VIII totals only twenty-eight. The series is probably too small to permit any definite conclusions. However, the data as we have them do not show any correlation between the completeness of the sympathectomy as measured by the dermometer and the results in relief of pain (Figs. 2, 3, and 4). This is not to be interpreted as indicating that one should be satisfied with anything less than a total denervation of an involved extremity. It is our definite feeling, although we have no proof, that one should always completely denervate the involved extremity if one wishes to get the best results from sympathectomy in the treatment of causalgia. Further, if a patient with true causalgia fails to obtain a satisfactory result following sympathectomy, estimation of the completeness of the operation should be done. The dermometer offers a convenient method. If the sympathectomy is incomplete, reoperation should be considered.

There has been offered, by Mayfield and Devine,[7] an explanation for the possible occurrence of poor results following sympathectomy. They state that

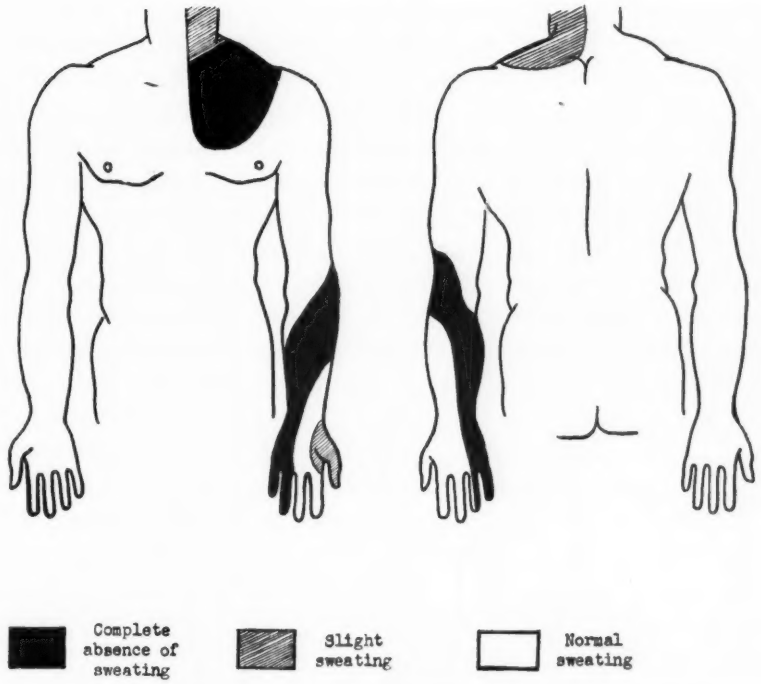

Fig. 2.—Complete relief of pain (Class I) after incomplete (Grade III) dorsal sympathectomy.

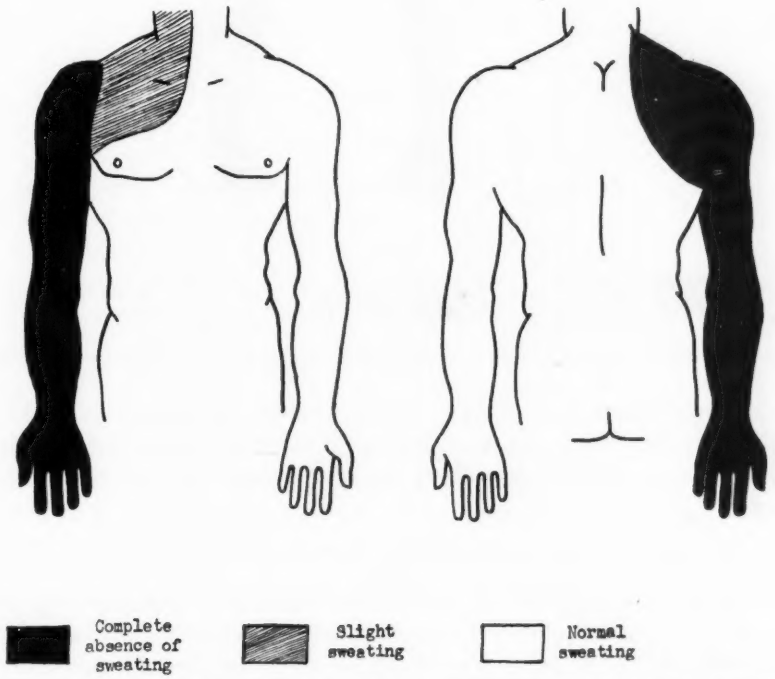

Fig. 3.—Incomplete relief of pain (Class III) after complete (Grade I) dorsal sympathectomy.

it is necessary to sympathectomize the area of the wound in order to produce the desired effect. Yet, they make three other pertinent assertions: (1) they state that all their patients with lower extremity causalgia had wounds proximal to the knee; (2) they state that their usual procedure is the removal of the second and third lumbar sympathetic ganglia, or the second, third, and fourth, which others agree usually sympathectomizes the lower leg, not the thigh; (3) in their experience all patients except one had satisfactory relief of pain. The conclusion is inescapable that rarely could they have sympathectomized the wound in the case of the lower extremity, and yet rarely did they fail to relieve the pain. It is difficult to believe, in view of this, that failure to denervate the area of the wound is a cause for incomplete or poor relief of causalgia following sympathectomy.

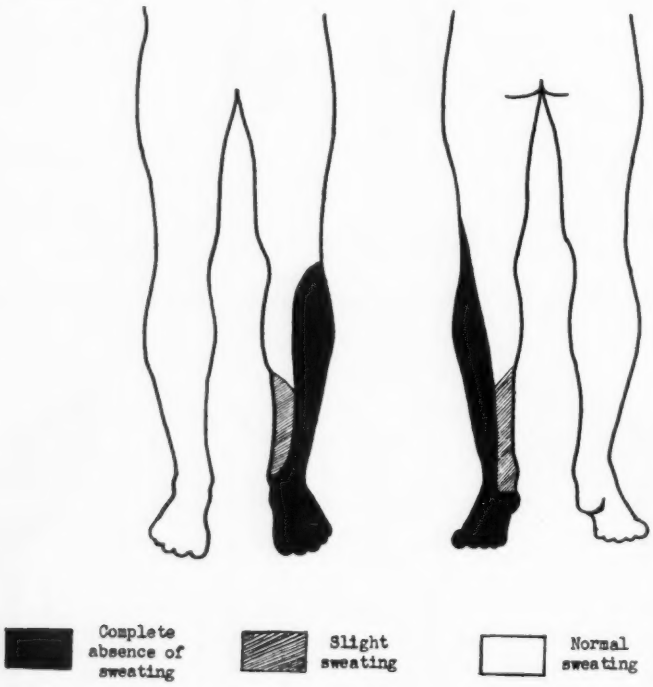

Fig. 4.—Complete relief of pain (Class I) after incomplete (Grade III) lumbar sympathectomy.

In summary, from the analysis of our results following sympathectomy, we can find no single factor to which one can point as a cause for some patients obtaining complete relief, and others obtaining only partial relief from this procedure.

RESULTS OF RESECTION OF NEUROMA AND GLIOMA

In the group of patients with typical causalgia, there are five cases in which resection of the neuroma and glioma of the involved nerve was performed because at exploration of the nerve the anatomic lesion found demanded resection and end-to-end anastomosis. Four of this group have not had sympathectomy, while the fifth is the previously referred to individual who failed to obtain relief from an incomplete sympathectomy performed prior to nerve

surgery. The five patients all showed typical lower extremity causalgia in the tibial nerve distribution. In the two patients so tested prior to nerve surgery, procaine block of the lumbar sympathetic ganglia gave a good relief of pain for from five to thirty minutes.

In two patients, one of whom had severe causalgia and the other of whom had moderate causalgia, complete relief of pain followed resection of the neuroma and glioma of the sciatic nerve; in a third there was some relief of the burning—enough so that the patient did not require subsequent sympathectomy. The fourth patient had some improvement in the causalgia for six weeks after neurorrhaphy of the sciatic nerve, but following this period the pain returned in its original intensity. He is now under consideration for sympathectomy. The fifth patient, previously mentioned, has had no relief from the tibial neurorrhaphy, and is to have a second sympathectomy through a high, anterior, transverse incision.

This series of cases is very small, and no definite conclusion can be drawn from it. However, together with the experience in World War I[19] that injection of 60 per cent alcohol into the involved nerve at or proximal to the level of the lesion sometimes produced immediate and apparently lasting relief of causalgia, it does suggest that resection of the neuroma and glioma of the involved nerve may on occasions bring about complete relief of pain. Thus, in cases with clinically complete nerve lesions and mild or moderate causalgia in the distribution of this nerve, it is probably wise to explore the nerve lesion first, particularly in the case of the lower extremity. If the lesion found in the nerve itself demands resection, it should be resected. Some patients so treated may be relieved of pain and thus not require sympathectomy. Those who continue to have pain should subsequently be subjected to sympathectomy.

SUMMARY AND CONCLUSIONS

1. Causalgia is a definite pain syndrome, associated with injury to a peripheral nerve containing sensory fibers.

2. The pathogenesis of the syndrome is not known.

3. It is not certain that causalgia occurs only in incomplete anatomic lesions.

4. The data on fifty-two cases of causalgia and nine of atypical post-traumatic painful states are reviewed. The clinical characteristics of causalgia are enumerated.

5. There are cases of post-traumatic painful extremity associated with a lesion of a peripheral nerve which differ from true causalgia to varying extents; occasional cases are distinguished from this syndrome only by their failure to be aggravated by disquieting factors in the individual's environment.

6. The pain of causalgia is usually relieved or abolished by adequate sympathectomy. There is no relation between the completeness of the relief and any known factor.

7. Resection of the neuroma and glioma of the involved nerve, particularly in the lower extremity, occasionally provides relief of the causalgia.

NOTE: Since completion of this manuscript, seventeen additional patients with true causalgia were satisfactorily treated by dorsal or lumbar sympathectomy, complete in each instance (Grade I or II by dermometer study). Clinical data and results from surgery are parallel to those just described.

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BENIGN CAVERNOUS HEMANGIOMA OF THE SPLEEN

Literature Review and Case Report

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BENIGN cavernous hemangioma of the spleen is rare. We have been able to find reports of only thirty-one cases in the literature which appear to us to represent this condition. Malignant lesions of the spleen are much more frequently reported. Smith and Rusk (1923)[1] collected 104 cases of primary malignant lesions of the spleen. Since this time other authors have reported smaller series.

Dowd (1915),[2] Akcakoyunlu (1938),[3] Cole and Forsee (1940),[4] and Pines and Rabinovitch (1942)[5] reported series of thirteen, twenty-one, twenty-three, and forty-two cases of benign cavernous hemangioma taken from the literature. When the cases in these series are thoroughly analyzed, it becomes evident that some do not represent true benign lesions.

Due to the lack of uniformity in classification, many cases labeled benign cavernous hemangiomas are in reality angiosarcoma, angioendothelioma, angioblastoma, simple sinusoid ectasia, etc. Many of the reported cases of benign cavernous hemangioma have been asymptomatic and were incidental autopsy findings. Other cases were surgical and presented a mass in the upper abdomen causing symptoms of pain, or were due to rupture (spontaneous or traumatic) with severe internal hemorrhage.

CASES IN THE LITERATURE

Hoge (1895)[6] reported the first successful splenectomy performed by McGuire for this condition. Dowd (1915)[2] collected twelve cases of splenic hemangioma from the literature and added one case of his own. Six of these were malignant and had metastases to other organs [Langhans (1879),[7] Homans (1897),[8] Theile (1904),[9] Jores (1908),[10] Ernst (1912),[11] and Dowd[2]]. Of the seven benign cases four were incidental autopsy findings [Albrecht (1902),[12] Theile (1904),[9] and Lubarsch (1905)[13]]. Splenectomy was successful in the remaining three cases [Martin (1909),[14] von Benckendorff (1908),[15] and Anzilloti (1913)[16]]. Steden (1924),[17] Näher (1925),[18] Schwartz (1930),[19] Wassilijeff and Pratassewitch (1930),[20] Zeno and Cid (1930),[21] Kellert (1932,[22] Palavecino and associates (1932),[23] Haines and McIlroy (1933),[24] Grove (1937),[25] Dawson (1937),[26] Schottenfeld and Wolfson (1937),[27] Akcakoyunlu (1938),[3] Nesler, Faber, and Leik (1939),[28] Cole and Forsee (1940),[4] and Stühlinger (1943)[29] each reported one case treated by splenectomy.

Krumbhaar (1927),[30] Mikami (1933),[31] Goldberg (1940),[32] Aronson and Fox (1940),[33] and Bostick (1945)[34] each reported one autopsy case. Only three of the six autopsy cases reported by Pines and Rabinovitch (1942)[5] appear to us to represent benign cavernous hemangioma.

Received for publication, April 8, 1946.

ETIOLOGY AND PATHOLOGY OF SPLENIC NEOPLASMS

In order to bring out the relationship of benign hemangioma to other splenic neoplasms, a brief discussion of the etiology and pathology seems warranted.

The pathogenesis of splenic neoplasms, as with neoplasms in other sites, is not known. However, there are certain factors that may be contributory. Smith and Rusk (1923)[1] in reviewing 104 cases of primary malignant lesions found a history of malaria in 13 per cent, syphilis in 4 per cent, trauma in 4 per cent, tuberculosis in 13 per cent, and typhoid fever occasionally. Secondary neoplasms are much more frequent than primary lesions. Krumbhaar (1927)[30] analyzed 6,500 autopsies from the Philadelphia General Hospital. In this group he found forty cases of splenic neoplasm (1.9 per cent of the tumors). Six were primary and only one represented a benign cavernous hemangioma.

Secondary neoplasms are rare when compared with this condition in other organs. This has been attributed to the absence of afferent lymphatics except for a few in the capsule, the sharp angle of the splenic artery, the pulsating action of the spleen in preventing lodgment of tumor cells, and to an intrinsic antagonistic effect of the spleen toward neoplastic growths. It has been shown experimentally that animals are more susceptible to tumor growth following splenectomy.

The spleen consists of four types of tissue capable of giving rise to neoplasm: the capsular and trabecular framework, the lymphoid element, the reticuloendothelial, and the vascular elements. The classification of splenic tumors is outlined in Table I.

TABLE I. TYPES OF SPLENIC TISSUE CAPABLE OF GIVING RISE TO NEOPLASM

TISSUE TYPE		BENIGN	MALIGNANT
Capsular and trabecular framework	fibrous, smooth	Fibroma	Fibrosarcoma
	muscle, nervous	Leiomyoma	Leiomyosarcoma
		Neuroma	Neurosarcoma
Lymphoid		Lymphoma	Lymphosarcoma
Reticuloendothelial		----	Endothelioma
			Reticulum-cell sarcoma
			Hemangioendothelioma
Vascular		Hemangioma	Angiosarcoma
		Lymphangioma	

Ewing[35] stated that endothelioma is the commonest primary type. Mallory,[36] however, believed that the lymphoblastomas are the commonest. MacCallum[37] pointed out that tumors of doubtful origin are likely to be labeled endothelioma. Smith and Rusk[1] in their study of a large series of primary malignancies of the spleen have considered lymphosarcoma to be the commonest malignancy that involves this organ and is usually associated with a generalized process.

The commonest secondary malignant tumor of the spleen is carcinoma (Krumbhaar).[30] Other secondary tumors are melanosarcoma, myeloma, lymphosarcoma, sarcocarcinoma, and endothelioma.

Cysts of the spleen should be given consideration in a discussion of the neoplastic lesions of this organ. They may be divided into three main types: (1) hemorrhagic cysts which arise from degenerated pulp or from angiomatous

areas. These may later develop into serous cysts. Traumatic subcapsular cysts are usually due to old hematomas and frequently contain cholesterin crystals. (2) Dermoid cysts due to epithelial and mesothelial inclusion. These may undergo carcinomatous change. (3) Parasitic cysts.

Small involution cysts may be due to trauma or inflammation. They are usually multiple and may be superficial or deep.

Hemangioma is a tumor comprised primarily of new blood vessels, the anlage of which is thought to arise from vascular disarrangement. The process begins by budding of endothelium from a segment of a vessel and results in the formation of new vascular spaces which are either capillary or cavernous in character. To a large extent hemangiomas have a closed vascular system and do not communicate freely with the normal vascular bed. They tend to displace rather than to replace the surrounding parenchyma.

Congenital nevi are thought to be the result of a vascular disarrangement and are not true tumors. They may, however, give rise to hemangioma. The finding of congenital nevi in the spleen should not be considered as constituting a new growth.

In simple sinusoid ectasia there is a free communication of the telangiectasis with the normal vascular spaces. This condition does not fulfill the criteria of hemangiomas.

CASE REPORT

M. A. B. (B13507), a 35-year-old married colored woman, was admitted to the hospital on July 7, 1945, with a complaint of an upper abdominal mass of four months' duration with rapid increase in size during the previous three weeks.

Past history revealed that she was seen for the first time in the medical clinic twenty-two months previously. Following examination a diagnosis of syphilis and aortitis was made. At this time the abdominal examination revealed slight epigastric tenderness and the spleen was palpated three fingerbreadths below the costal margin. The patient was referred to the health department for antisyphilitic therapy.

She did not report for treatment and was again seen two months before admission complaining of an upper abdominal mass of eight weeks' duration associated with pain radiating into the back. Examination disclosed a large mass in the left upper quadrant of the abdomen. It was felt that she had a pancreatic or splenic tumor and hospitalization was advised.

She returned for admission on July 7, 1945. The abdominal mass had increased rapidly in size. There were some digestive disturbances and constipation. During the previous three weeks she had been having an afternoon fever and was bedridden because of abdominal discomfort and pain in the back. On the day before admission she complained of hematuria. There was no history of trauma or malaria.

Examination revealed a temperature of 38.4° C., pulse 100, respirations 30, and blood pressure 160/108. The patient was an obese colored woman who did not appear ill. The abdomen was protuberant (Fig. 1, *A* and *B*). The lungs were clear. The heart was enlarged to the left and the rate and rhythm were regular. No murmurs were heard.

The abdominal examination revealed a large firm mass occupying the upper abdomen and left flank. It extended into the epigastrium and down to the level of the iliac crest. The mass was slightly movable and appeared to be cystic in the epigastric region. There was moderate tenderness in this area. The liver and kidneys were not palpated. Pelvic examination did not reveal any abnormalities.

A. *B.*

Fig. 1.

Fig. 2.

Fig. 1.—*A*, Preoperative, note the marked protuberance of the abdomen; the mass was cystic in the epigastrium. *B*, Patient ten days following operation.

Fig. 2.—Roentgenogram of the abdomen showing most of the detail obscured by a large soft tissue mass. The stomach is displaced to the right and the colon downward.

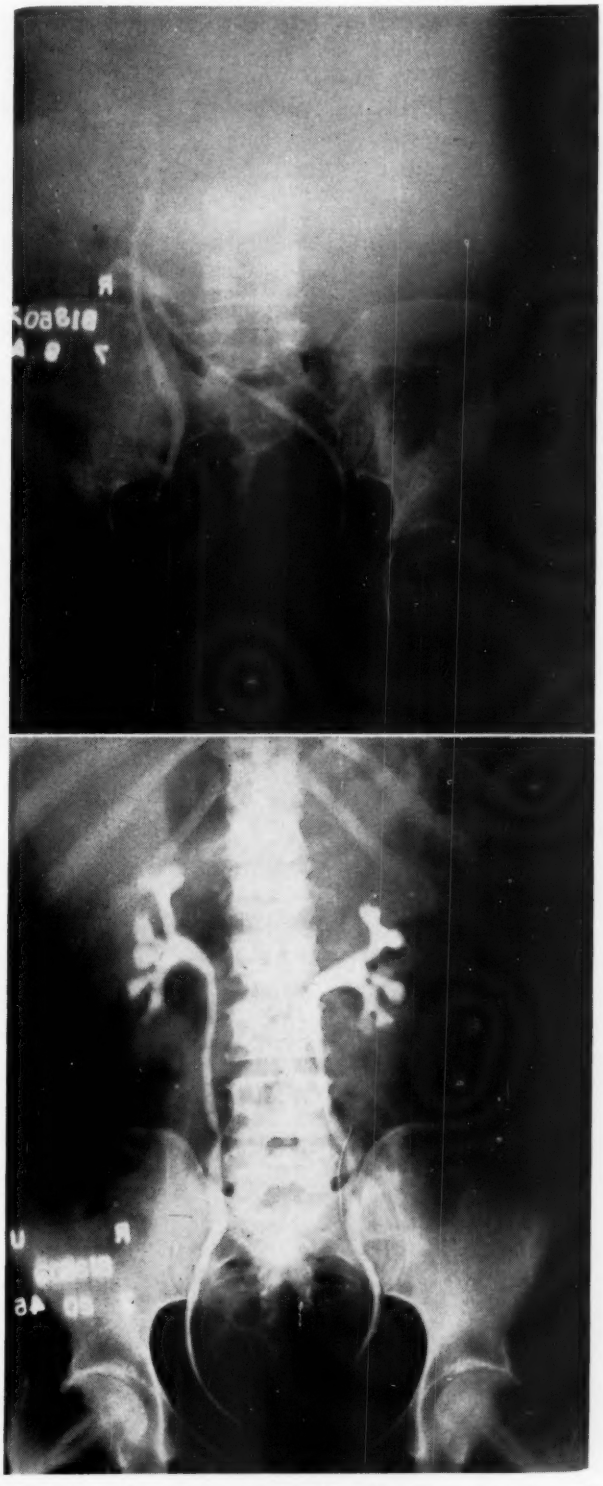


Fig. 3.—Preoperative and postoperative retrograde pyelograms showing displacement of the left kidney and return to a normal position following operation.

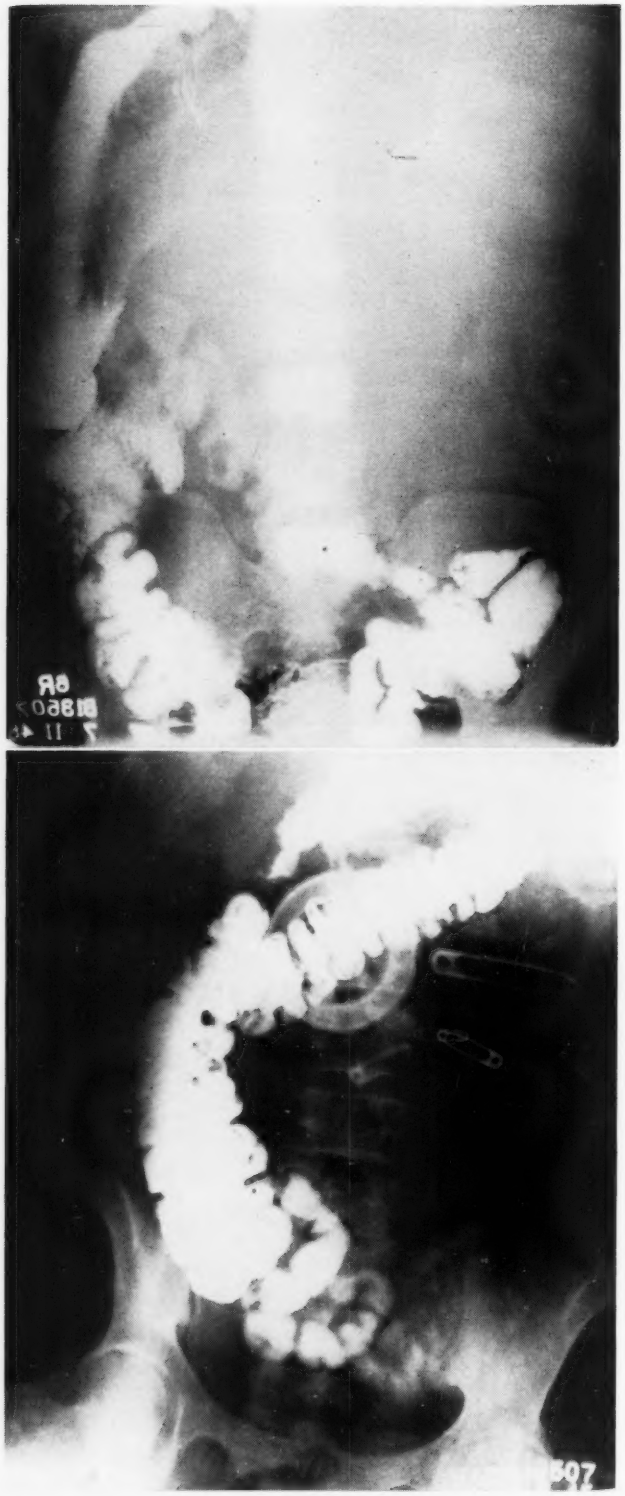


Fig. 4.—Preoperative and postoperative gastrointestinal barium studies showing displacement of stomach and colon and their return to a normal position following operation.

Laboratory findings were hemoglobin, 82 per cent; red blood cells, 4,080,000; and white blood cells, 14,000. Differential count showed 41 per cent polymorphonuclears, 44 per cent small lymphocytes, 8 per cent large lymphocytes, 2 per cent eosinophiles, 1 per cent basophiles, 1 per cent stabs, and 3 per cent monocytes. The serology test for syphilis was positive. Total serum proteins were 8.3 Gm. per cent, the albumin being 3.1 Gm. per cent and the globulin 5.2 Gm. per cent. The urine had a trace of albumin on occasions. Kidney function tests were normal and the nonprotein nitrogen was 24 mg. per cent. Stool examination was negative.

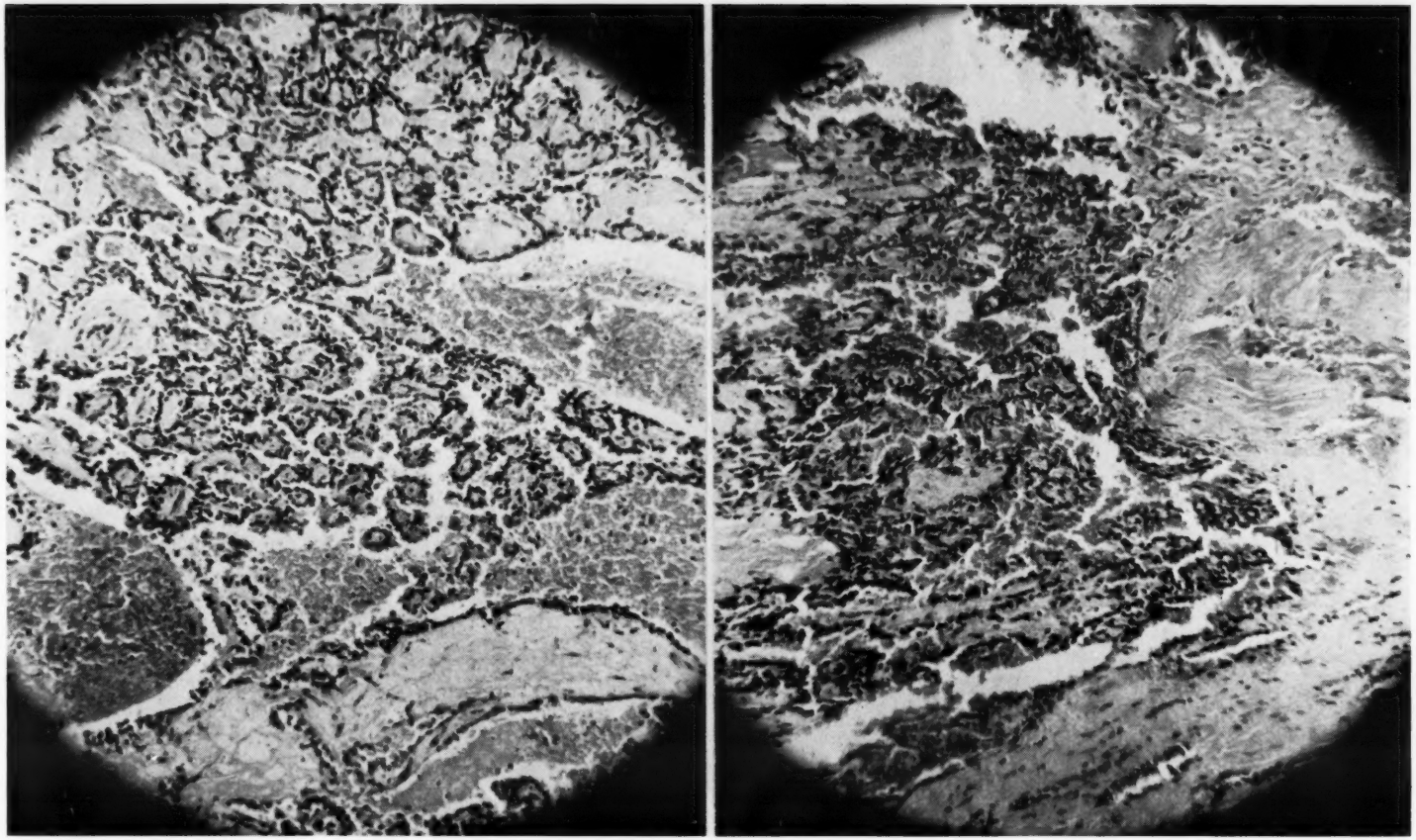
Roentgenogram of the abdomen showed most of the abdominal detail obscured by a large upper abdominal soft tissue mass (Fig. 2). Fluoroscopy of the chest revealed elevation and poor movement of the diaphragm. The heart was in a transverse position and there was slight ventricular enlargement.

With retrograde pyelograms the left kidney was found displaced by a mass into the right lower quadrant (Fig. 3). Gastrointestinal series showed the stomach pushed to the right and the colon displaced far downward (Fig. 4). The electrocardiograph revealed sino-auricular tachycardia with left axis deviation and an isoelectric T_4.

Fig. 5.—The tumor, including the aspirated sanguineous fluid, weighed 13,130 Gm. Approximately 12,000 c.c. of fluid were removed from the cystic mass before extirpation was carried out. The dimensions were 28 by 28 by 20 cm.

On July 12, 1945, the patient was operated upon and a large cystic mass occupying almost three-fourths of the abdominal cavity was found. This mass arose from the inferior medial aspect of the spleen which was markedly compressed. Approximately 12,000 c.c. of bloody fluid were aspirated from the cystic mass before removal was carried out. The mass and compressed spleen were inseparable.

On pathologic examination the lesion was found to be a benign cavernous hemangioma arising from the spleen. There was a large cyst associated with the hemangioma. The tumor weighed 13,130 Gm., the largest yet reported, and had a diameter of 28 cm. The patient made an uneventful recovery and was discharged from the hospital on July 23, 1945, eleven days postoperatively. A recent follow-up study revealed that she was in good health.



A. *B.*

Fig. 6.—Microscopic examination. *A*, Note the large cavernous and capillary blood spaces lined by endothelium. There are areas of hyalinization and evidence of developing new vascular spaces. *B*, Sections taken through cyst wall showing relationship to tumor.

COMMENT

The diagnosis of benign cavernous hemangioma may be extremely difficult. It was an incidental finding in eleven of twelve autopsy cases. In the other case there was rupture of the lesion with death from severe hemorrhage. In the nineteen patients treated surgically, three had spontaneous rupture with serious hemorrhage into the abdominal cavity. (Haines and McIlroy,[24] Nesler, Faber, and Leik,[28] and Cole and Forsee[4].) A diagnosis of perforated gastric ulcer was made in two and appendicitis in one. The other surgical cases presented the following combination of signs and symptoms: abdominal mass or splenomegaly, pain, dyspnea, dysphagia, gastrointestinal disturbances, and anemia.

Splenic hemangioma should be suspected in patients with splenomegaly unrelated to a general disease process. When rupture (spontaneous or traumatic) occurs, shock, pain, and signs of generalized peritoneal irritation are usually present. Shock must be combated and immediate operation is imperative.

SUMMARY

We have been able to find only thirty-one cases in the literature that appear to us to represent true benign cavernous hemangioma. Another case is reported. In nineteen of the reported cases in the literature, treatment was by splenectomy. Twelve were autopsy findings.

Some of these lesions may attain an enormous size and undergo cyst formation. In four of the cases there was spontaneous rupture with severe hemorrhage into the abdominal cavity. Thorough microscopic examination of many of the traumatic cysts of the spleen might disclose an underlying hemangiomatous lesion and unless this is kept in mind cases may be missed.

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CYSTADENOMA OF THE PANCREAS

With Presentation of One Case and Review of Twenty-Eight Cases Collected From the Medical Literature

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CYSTADENOMA of the pancreas is a strikingly distinct pathologic entity. It is characterized by slow growth, absence of early symptoms, and later development of a palpable tumor, upper abdominal pain, and weight loss. Occasionally diabetes mellitus is an associated finding. Pathologically it is distinguished as a benign, multilocular, cystic, adenomatous neoplasm which most often originates from the tail or body of the pancreas. That it is an uncommon tumor is evidenced by the fact that there are only about sixty cases reported in the medical literature. The following case illustrates the condition and demonstrates the efficacy of surgical excision.

CASE REPORT

Mrs. D. M., a white woman, aged 65 years, was examined at the Billings Clinic on March 6, 1945. The chief complaints were upper abdominal pain and weight loss.

The patient was of Italian descent and had come to America from Italy at the age of 18 years. She had had five uneventful pregnancies. The menopause occurred in 1932. There was no known family history of tuberculosis, diabetes, cancer, or other significant diseases. She had had the usual childhood sicknesses but aside from this had been well until December, 1940. At this time the patient first developed pain in the upper abdomen, associated with a moderate loss of weight. It was ascertained at this time that the patient had cholelithiasis and mild diabetes mellitus. In May, 1941, cholecystectomy was performed. The gall bladder contained many large and small stones. The postoperative convalescence from this operation was marred by the development of bronchopneumonia from which she eventually made a complete recovery. The diabetes continued to be mild after this operation and was controlled in the hospital by dietary restrictions alone. After dismissal it became necessary to give her a more liberal diet and ten units of insulin daily.

When seen on March 6, 1945, the patient stated that the complaints for which cholecystectomy had been performed had not been relieved by the operation. In the intervening four years the epigastric and upper abdominal pain had been present constantly. It was intermittently more severe and radiated through to the region of the upper lumbar and lower dorsal spine. The pain had become progressively more intense and for many weeks prior to examination the patient had been confined to bed the majority of the time. Ingestion of food seemed to make the distress somewhat worse. There was no selective dyspepsia. In the four and one-half years since the onset of the illness the patient had lost fifty pounds in weight. There was a concomitant loss of strength and general debility. Food ingestion had been slightly restricted.

Physical examination revealed a short stocky woman who showed evidences of severe recent weight loss. The blood pressure was 180 mm. of mercury systolic and 90 mm. of mercury diastolic. The temperature was 98.6° F.; the pulse, 72 per minute. There were upper and lower artificial dentures. A small nodular goiter was palpable but there were no evidences of hyperthyroidism. The heart was moderately enlarged. No murmurs were audible. Auscultation of the lungs revealed a few basal râles. The abdomen was obese. There was an old surgical scar in the right upper quadrant of the abdomen. In the left

Received for publication, April 10, 1946.

upper abdominal quadrant a distinct nodular mass was palpable. It was rounded and approximately 12 to 14 cm. in greatest diameter. The mass moved with respiration and showed considerable mobility in the longitudinal axis of the body. The mass itself was only slightly tender. The point of greatest tenderness was in the epigastrium above and to the right of the tumefaction. Pelvic examination revealed a moderate cystocele and rectocele with associated mild prolapsus uteri. Rectal examination was not informative. There was no significant deformity of the spine. Fist percussion over the upper lumbar and lower dorsal vertebrae, and in the left flank area elicited abnormal tenderness. There were mild varicosities of both lower extremities. The tendon reflexes were equal and active.

Erythrocytes numbered 4,900,000 per cubic millimeter; leucocytes, 6,000 per cubic millimeter. Hemoglobin estimation was 17.2 Gm. per 100 c.c. (110 per cent). Urinalyses were essentially negative. The serologic test for syphilis was negative. The blood sedimentation rate was 10 mm. in one hour. The fasting blood sugar was 134 mg. per 100 c.c. The blood urea nitrogen was 14.2 mg. per 100 c.c. Roentgenograms of the colon following the administration of a barium enema revealed normal contours and no evidence of intrinsic disease. Roentgenograms of the stomach following the ingestion of barium were negative. There was no gastric retention. Stereoscopic roentgenograms of the chest revealed no significant abnormalities. Roentgenograms of the dorsal and lumbar spine were not informative except for the presence of minimal changes characteristic of the senescent type of arthritis. Intravenous urograms showed loss of some of the fine renal markings but no significant deviation from the normal.

In view of the noninformative roentgenologic findings it was reasoned preoperatively that the tumefactive intra-abdominal lesion was probably situated in the tail of the pancreas. That the spleen or a mesenteric cyst was the site of origin of the tumor was also considered. Operative intervention was advised and accepted. The diabetic state was still mild and no evidence of acidosis had occurred although the patient had neglected dietary care and frequently had had glycosuria before admission to the hospital.

On April 10, 1945, under nitrous oxide, oxygen, and ether anesthesia exploratory laparotomy was performed. The abdomen was opened through a long primary upper left subcostal type of incision dividing the left rectus muscle. Primary exploration of the liver, stomach, duodenum, small and large intestine, and pelvic organs was negative. The gall bladder had been removed previously. In the left upper quadrant bulging through the gastrocolic omentum was a large tumor mass. It displaced the transverse colon slightly downward and the fundus of the stomach upward. The gastrocolic omentum was divided and the tumor exposed. It presented a most unusual appearance. It was about the size of a grapefruit and consisted of many smooth encapsulated grapelike nodulations which varied in color from blue to deep purple. The mass was adherent posteriorly to the splenic vein. It arose from the tail of the pancreas and had replaced this portion of the pancreas and some of the distal portion of the body of the pancreas. The tumor, a segment of the splenic vein, and a distinct cuff of normal pancreatic tissue were then removed in toto. The remaining stump of the pancreas was closed with interrupted sutures of chromic catgut and fine silk. That portion of the pancreas which remained consisted of the entire head and as much of the body as extends approximately 4 cm. to the left of the superior mesenteric artery. At the conclusion of the operation splenectomy was performed and 5 Gm. of sulfathiazole were dusted intraperitoneally. Two Penrose drains were inserted down to the inverted end of the pancreas and the abdomen was closed.

The specimen consisted of a lobulated tumor mass 8.5 by 10 by 8 cm. in diameter. The cut section was multilocular and contained innumerable small cystic cavities, the largest 1.5 cm. in diameter. These spaces were filled with gelatinous fluid which varied in color from amber to deep red and purple. In one portion there was a small cuff of tissue that proved to be, grossly and microscopically, essentially normal pancreatic tissue. The numerous walls of the multilocular cysts were composed of dense fibrous tissue. The cavities were lined with flat cuboidal epithelium. The picture was that of benign cystadenoma of the pancreas. Another portion of the specimen consisted of an essentially normal spleen by gross and microscopic examination.

The convalescence of the patient was marred by the development of a small pancreatic fistula. For several weeks postoperatively a thick fluid escaped from the wound. Four weeks after the operation the patient became quite ill with fever (temperature 103° F.) and considerable abdominal pain. This was occasioned by removal of the drains. Following incision and drainage of a small collection of fluid beneath the original incision the patient progressed rapidly. Eight weeks after the operation the wound had healed completely and the patient was ambulatory and able to attend to some of her usual household duties.

On Dec. 7, 1945, nine months after operation the patient returned for a thorough résumé of her physical status. At this time she was feeling well and had only the minor complaint of slight weakness in the extremities. She had gained twenty pounds in weight and had resumed all her former duties. Abdominal examination was negative. There was no evidence of any mass or tenderness. A glucose tolerance test was performed using the Exton-Rose technique. The fasting blood sugar was 145 mg. per 100 c.c. and the highest blood sugar at the end of one hour was 316 mg. The patient had not been following the diet and had been taking insulin irregularly. She had had no glycosuria before breakfast in spite of the irregular habits. The diabetic state was essentially unchanged by operation.

DISCUSSION

Pathologic Considerations.—Cystadenoma of the pancreas is a true neoplasm composed of multiple cystic cavities lined by cuboidal or columnar epithelium. The cysts contain fluid which may be thin and watery in consistency but which more often is thick and viscid or gelatinous. Sometimes the fluid is light yellow in color but more often, and especially when it is of a viscid consistency, it is dark brown or purple or red, an effect which is said to result from hemorrhage into the spaces (Figs. 1 and 2). The cyst fluid is said to contain no ferments.[7] The epithelial lining of the spaces is characteristically low cuboidal or columnar in type, and often there are no papillary infoldings (Fig. 3). When papillary projections are found Dockerty believes that they should be classified as malignant even though the usual microscopic criteria for malignancy are minimal. The recorded experiences of Speese and Young in which such "benign" papillary cystadenomas invaded surrounding structures after incomplete excision or underwent frankly malignant degeneration lend strength to this viewpoint. The more common practice, however, has been to classify these papillary cystadenomas of the pancreas as benign in the absence of direct microscopic evidence of malignancy in spite of their occasional aberrant invasive properties.

In some cysts which grow to very large size, the epithelial lining may be completely destroyed. If smaller spaces are found surrounding the large cyst which continue to retain their epithelial linings, the condition may still be classified as cystadenoma. When none of the fluid-filled cavities are lined with epithelium, the condition is some other than cystadenoma.

Cystadenomas of the pancreas are usually well encapsulated but they may be densely adherent to surrounding structures. Most often they are embedded in and have replaced the pancreatic tissue. Occasionally cystadenomas are pedunculated and attached to the pancreas by only a narrow stalk. The blood supply is usually profuse. Numerous large dilated veins are commonly found coursing over the capsule of the tumor. All variations in size have been observed from small tumors "about the size of a walnut" to very large tumors. Kennard

Fig. 1.—Cystadenoma of the pancreas; specimen obtained at operation upon a 65-year-old white woman. The tumor occupied the tail and major portion of the body of the pancreas.

Fig. 2.—Cut surface of the same tumor depicted in Fig. 1. The tumor is composed of many large and small cystic epithelial lined cavities which contain multicolored gelatinous fluid.

reported a case in which the mass measured 15 cm. in diameter and weighed 2,050 Gm. In one of the cases presented by Bowers and associates, the tumor measured 18 by 12 by 13 cm.

The stroma is often composed of narrow connective tissue septa. Sometimes the septa are broad bands in which hyalinized areas may be seen. Smooth muscle fibers may be present in the stroma. The source of these, according to Brunschwig, has been stated as being derived from previously patent vessels and pancreatic ducts. In the case reported by Carling and Hicks, areas of calcification were encountered. Small epithelial lined spaces of microscopic size may be scattered throughout the wider connective tissue septa.

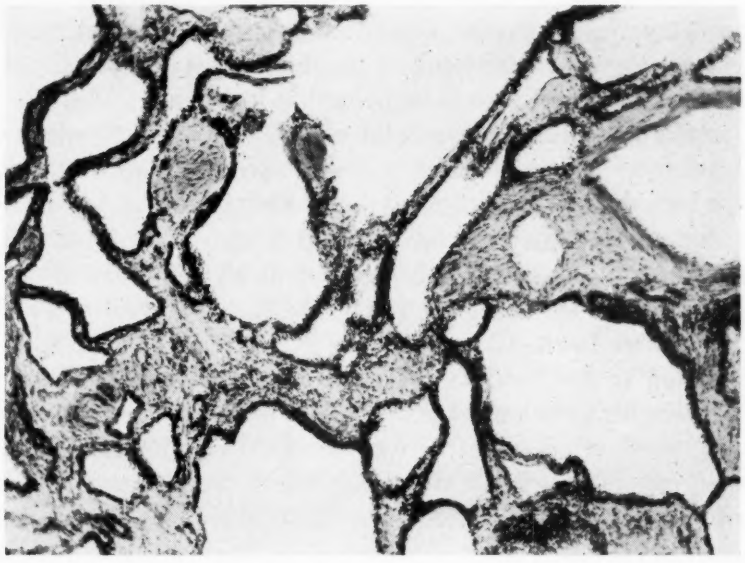

Fig. 3.—Microphotograph showing the cystic spaces lined with low cuboidal epithelium and no papillary infoldings. The stroma is composed of dense fibrous tissue (×45).

Clinical Considerations.—Pancreatic cystadenomas occur very infrequently. In 1930, Judd, Mattson, and Mahorner reported that out of 723,397 patients admitted at the Mayo Clinic there were only eighty-eight surgically explored cases of pancreatic cysts of all types. In a subsequent report from the Mayo Clinic by Mahorner and Matson, of 108 cysts of the pancreas only two were found to be cystadenomas. In spite of the rarity of the lesion a review of the literature has enabled us to compile twenty-seven surgically explored cases of cystadenoma of the pancreas. These plus the case herein presented give a series of twenty-eight cases from which to draw conclusions. Many more reports have been perused but because of incomplete data or inconclusive evidence as to the pathologic entity under discussion are not included.

Of the twenty-eight cases, apparently complete removal of the tumor was carried out in twenty-one cases. Incomplete excision was performed in three cases, biopsy alone in three cases, and abdominal exploration with subsequent post-mortem examination in one case. In twenty-six cases in which the result

of operation is known there were eight postoperative deaths (31 per cent). Four of these deaths resulted from abdominal exploration with or without biopsy of the tumor without any attempt being made to remove the growth. In twenty cases in which the tumor was removed and the outcome is known, there were four postoperative deaths (20 per cent). In the fourteen cases cited by Muller in which excision was performed, there were no immediate postoperative deaths, but in three instances death occurred later, possibly associated with the operation. In Brunschwig's series of four cases from the University of Chicago clinics one death occurred. This fatality occurred following radical pancreaticoduodenectomy for an extensive tumor of the head of the pancreas.

The average age of the twenty-eight patients was 48 years. The youngest patient was 17 years of age, the oldest 76. It is thus apparent that the condition is most frequently encountered in the middle age group. Gruber is said, however, to have described two cases occurring in infants. There is a striking disparity in the distribution between the sexes. Of the twenty-eight cases only three (11 per cent) were in males. The greater tendency for women to be affected has been demonstrated previously by Kleinschmidt.

Cystadenomas are most commonly found in the tail and body of the pancreas. In twenty-seven cases of this series in which the situation of the tumor was stated, nine were located in the tail of the pancreas, two involved the body and tail, eight were in the body alone, one arose from the head and body, and seven originated in the head of the pancreas. In Kleinschmidt's review of twenty-one cases, two tumors arose in the mid-portion, four involved the entire gland, and the remaining fifteen were in the tail. The fact that the preponderance of these tumors arise in the distal portions of the pancreas (tail and body) has contributed to the good surgical results obtained. It is technically much easier to remove the tail or body of the pancreas than the head.

The most important clinical finding is a palpable upper abdominal mass. Of the twenty-seven cases with complete data a palpable tumor was present in all. The mass is most frequently felt above and to the left of the umbilicus in the left hypochondrium. When the tumor is situated in the tail of the pancreas it may sometimes disappear beneath the left costal margin and not be again palpable until the patient assumes the erect position or inspires deeply. Often the tumor is rather freely movable in the longitudinal axis of the body. X-ray studies give no direct information as to the origin of the tumor. Roentgenographic examination of the stomach following the ingestion of barium may reveal a defect in the posterior and inferior aspect of the gastric shadow as a result of extrinsic pressure. Roentgenograms of the colon following the administration of a barium enema may show lateral or downward displacement of the transverse colon or splenic flexure from the pressure of the neoplasm. Urograms are usually not informative except as they eliminate the kidney and adjacent retroperitoneal area as the source of the tumefaction. In the case herein reported, after all manner of x-ray examinations had been performed, there was still considerable doubt preoperatively as to whether or not the palpable tumor

arose from the pancreas or was a ptosed spleen or a mesenteric cyst, a dilemma which others reporting this type of case have also encountered.

The patient may have no complaints other than the presence of a palpable intra-abdominal tumor, but in the majority of the cases in this series upper abdominal distress or pain was present. In the case herein reported the pain was located in the epigastrium well to the right of the tumor. It was diurnal, severe, and radiated through to the back with such intensity that roentgenographic examination of the spine was undertaken to eliminate the possibility of pathology in the vertebral column. In other cases the pain and distress were much less severe. Dyspeptic symptoms also frequently have been described in association with this type of tumor.

It has been adequately demonstrated that the pancreas may harbor a cystadenoma for many years without producing symptoms. Such tumors often grow very slowly and may be symptomless for long periods of time. Brunschwig has recorded the case of a woman, age 62 years, who according to her own statement had been aware of a palpable epigastric mass for ten years. For nine years it had apparently caused no inconvenience. Subsequently, however, she lost thirty pounds in weight and developed diabetes mellitus. At operation a cystadenoma of the head of the pancreas measuring 7 by 4 by 3.5 cm. was removed. With increasing size of the tumor, pain and weight loss ensued. The patient whose record is herein reported lost fifty pounds in weight. Many other examples of subjects who sustained weight losses of thirty, forty, and fifty pounds are available. This weight loss usually occurs in spite of apparently adequate food intake.

Occasionally the first symptoms of a cystadenoma of the pancreas will be those of an acute intra-abdominal catastrophe initiated by hemorrhage from the tumor. A girl, aged 17 years, who had been acutely ill for five days was subjected to emergency laparotomy. At operation the peritoneal cavity was found to contain a large quantity of fresh blood. The source of the hemorrhage was a large cystadenoma of the pancreas. The patient died postoperatively. The post-mortem diagnosis was papillary adenocystoma of the pancreas with hemorrhage.[3] Pettinari's case is also of interest in regard to the association between these tumors and acute abdominal symptoms. His patient, a 70-year-old woman, was suddenly seized with very severe epigastric pain following breakfast of coffee and milk at 9 A.M. That night upon admission to the hospital, emergency laparotomy was performed under the diagnosis of perforated gastric ulcer. The stomach was found to be negative but the pancreas was markedly inflamed and edematous. There were no areas of fat necrosis present. A tumor mass "about the size of a walnut" was found in the region of the neck of the pancreas and was resected with a cuneiform section of pancreatic parenchyma. The abdomen was closed with drainage. A temporary fistula including bile developed and the patient completely recovered. Histologic study of the excised tumor revealed a typical cystadenoma with marked acute leucocytic infiltration of the excised pancreatic parenchyma. Pettinari is of the opinion that there was no causal relationship between the tumor and acute pancreatitis. The latter was assumed to be of "hematogenous origin."

Twenty-two of the twenty-eight patients did not have diabetes preoperatively. In none of these was the development of postoperative diabetes recorded. This is as expected for Dragstedt has shown that diabetes does not follow subtotal pancreatectomy even if only a very small portion of pancreatic tissue remains. It is significant that six of the twenty-eight did have diabetes preoperatively. In none of these did the diabetes result from destruction by the tumor of a large enough amount of pancreatic tissue to produce diabetes. Possibly in all it was a concomitant unrelated affection. Further study is necessary to settle this point. It might be assumed that the presence of the neoplasm in the pancreas could exert a depressant action on the diabetogenic functions of the pancreas as a whole. If this were the case, removal of the tumor should relieve or ameliorate the diabetic state. Bowers and co-workers recorded the case of a 37-year-old diabetic white woman who, after excision of a cystadenoma of the tail of the pancreas, required much less insulin for satisfactory control of the diabetes mellitus. A similar improvement did not eventuate in our case and others have likewise failed to note it. Carling and Hicks stated that the diabetes mellitus of their patient was much more severe following excision of the tumor. Why six of twenty-eight patients (21 per cent) with cystadenoma of the pancreas had diabetes mellitus must for the present be unexplained. Possibly when a larger series of cases can be collected, the incidence of diabetes among persons with cystadenomas of the pancreas will be more nearly that of the population in general.

Surgical Considerations.—Brunschwig and others have, after large experience, written so beautifully of the technical aspects of pancreatic surgery that it little behooves us to enter this discussion. It is apropos, however, to note here that marsupialization of pancreatic cystadenomas is ordinarily poor treatment. A number of failures and poor results of this type of operation have been recorded. It is permissible only when removal is impossible and if there is one predominantly large cyst which if drained will lead to considerable diminution in the size of the tumor. Excision, enucleation, or resection is the surgical treatment of choice.

SUMMARY

1. A surgically treated cystadenoma of the pancreas is reported and a series of twenty-eight cases collected from the medical literature reviewed.

2. Pathologically cystadenoma of the pancreas is a benign, multilocular, cystic, adenomatous neoplasm which most often originates from the tail or body of the pancreas.

3. Clinically this tumor is characterized by slow growth, absence of early symptoms, and later development of a palpable tumor, upper abdominal pain, and weight loss.

4. Pancreatic cystadenomas occur much more frequently in women than in men (ratio 8:1).

5. Six of twenty-eight patients in this series had associated diabetes mellitus.

6. Complete surgical removal of the tumor is the treatment of choice.

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ANEURYSM OF RENAL ARTERY

Report of Additional Case

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ANEURYSM of the renal artery is, indeed, a rare clinical and pathologic entity. One need only read the excellent review of the literature by Lowsley and Cannon[1] to establish its rarity. In their review of the entire medical literature they found only seventy-four cases. They reported a case of their own (diagnosed preoperative) making a total of seventy-five cases. Being diagnosed preoperatively, their case makes the twelfth case to be so diagnosed in the "history of the world." Since the excellent presentation by Lowsley and Cannon, however, another case has been reported by Levine; (2) it was diagnosed preoperatively and successful operation was done.

It is the purpose of this paper to present another case of aneurysm of the renal artery diagnosed preoperatively, thus bringing the total to seventy-seven reported cases, fourteen of which were diagnosed preoperatively. The etiology, pathology, signs, and symptoms, so well presented in these references need not be included here.

CASE REPORT

B. G., aged 44 years, was seen for the first time Nov. 1, 1945, complaining of pain in the right flank and right upper quadrant for the last three years. At times pain was accompanied by considerable gaseous eructations not related to food intake or type of food, although fatty foods were voluntarily avoided. In the last several weeks the pain had become more constant and severe. There was no nausea or vomiting. Bowel movements were regular and of normal color. There were no associated genitourinary complaints.

Past history was essentially negative except for a repair of an umbilical hernia eighteen years before, and the uneventful births of nine healthy infants. Review of systems was otherwise entirely negative.

Physical examination revealed a short, obese white woman appearing in good health. The abdomen was obese and pendulous. A four-inch well-healed vertical cicatrix was present just to the right of the umbilicus. The abdomen was soft throughout and no masses or soft organs were palpable. There was slight but persistent costovertebral tenderness on the right side. Pelvic and rectal examinations were negative. The blood pressure was 160 systolic, and 88 diastolic. Laboratory work-up, including a Wassermann test, was negative except for a trace of albumin and 8 to 10 white blood cells in the urine.

Roentgenograms were made of the gall bladder and kidneys. The gall bladder functioned normally. The roentgenograms showed a wreathlike calcified shadow lying outside the well-outlined gall bladder. Intravenous pyelograms revealed this wreathlike shadow to be lying outside of and medial to the right kidney. Both kidneys functioned normally. A diagnosis of aneurysm of the right renal artery was made.

When the seriousness of this condition was explained to the patient, she readily consented to operative treatment. She was admitted to St. Elizabeth Hospital and on November 7, under general anesthesia, the right kidney and pedicle were exposed through the usual lumbar approach. The pedicle was carefully mobilized and examination revealed a pulsating mass in the hilus of the right kidney.

Received for publication, April 25, 1946.

The preoperative diagnosis having been absolutely substantiated, the kidney was removed in the usual manner, reparative operation being out of the question. The wound healed per primam and the convalescence was uneventful. She was allowed out of bed early with no ill effects and was discharged twelve days postoperatively. Since the nephrectomy she has been free of symptoms.

Description of Specimen.—Grossly the kidney appeared normal in every respect. At the bifurcation of the renal artery on the posterior aspect, there was a saccular arterial dilatation. It was reddish yellow in color, firm to touch, and measured 2 by 1.5 by 1.5 cm. The wall of the sac contained calcified plaques. The cut surface of the kidney was normal; the pelvis and calices were not dilated. Microscopic examination of the wall of the sac revealed it to be a true aneurysm.

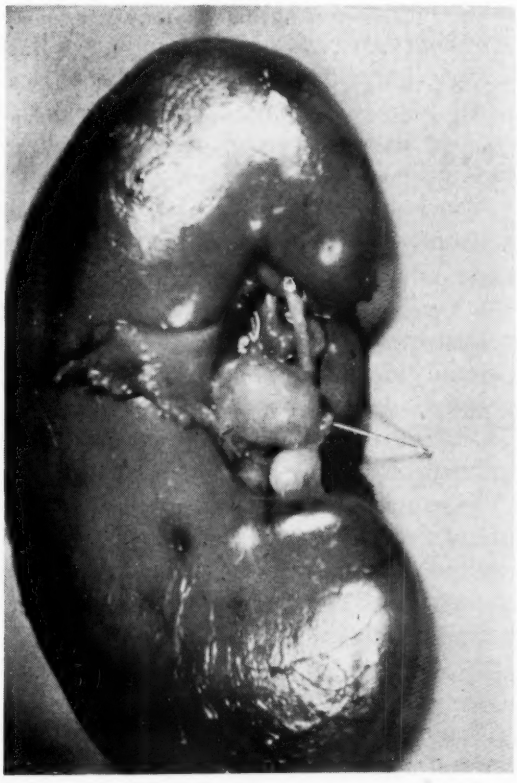

Fig. 1.—Surgical specimen showing probe in aneurysm.

SUMMARY

An additional case of true aneurysm of the renal artery is reported. This makes the seventy-seventh case reported, and the fourteenth case diagnosed preoperatively. A nephrectomy was performed through the usual lumbar approach, and the patient was entirely relieved of all symptoms.

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CLOSTRIDIAL WOUND INFECTIONS AND GAS GANGRENE

Arterial Damage as a Modifying Factor

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ONLY during time of war is the surgical profession properly conscious of the importance of gas gangrene and allied infections by the anaerobic clostridial organisms. The surgeons who returned from France at the close of World War I had abundant experience with it and most of them remained alert to its frequent occurrence in civilian surgical practice. For a younger generation of surgeons, World War II provided a similar experience and, it is hoped, a continued awareness of its seriousness, for indeed there is no condition in which a high index of suspicion and a prompt diagnosis have greater influence upon the outcome. The loss of life and limb which results from delays is a challenge which can be met only by maintaining constant rather than sporadic interest in this disease. Its occurrence in peacetime, vehicular and industrial accidents, as well as in association with senile or diabetic gangrene, is sufficiently common to warrant such continued attention. Here distinction is being made between clostridial wound infections, which are more or less localized processes having a hopeful prognosis under conservative surgical management, and gas gangrene, which is a diffuse disease carrying an immediate threat to life and urgently demanding radical surgery. This distinction has not always been clearly preserved. The course which a given case will follow is determined not so much by the nature of the invading organisms nor the particular tissues which they invade as it is by the state of adequacy of the arterial circulation. Vascular damage with incompetency thus becomes a very important consideration in prognosis and treatment of all cases of clostridial infection.

INCIDENCE

Advances in military surgery, notably early débridement of the wound, widespread use of the sulfonamides and of blood transfusion, and air evacuation of the wounded, resulted in a remarkable reduction during World War II in the incidence of anaerobic infection of wounds. The medical history of World War I, issued by the Surgeon General of the Army, recorded that battle wounds involving soft tissues only were complicated by gas gangrene in 10.8 per 1,000 cases, while those wounds which were associated with compound fractures showed this complication in 63 cases per 1,000. The complete figures for World War II are not available, but isolated reports from various theaters of operation are significant. Cutler and Sandusky's report of infection of this type in 18 per 1,000 wounds received in aerial combat is typical and is unusually interesting because of its bearing upon the concept of the essentiality of soil contamination as an etiologic factor. Jeffrey and Thompson reported that the British forces involved

Received for publication, April 9, 1946.

in the Italian campaign had gas gangrene in 10 per 1,000 casualties. Neal and Cole set the incidence at 15 per 1,000 among the casualties on a hospital ship supporting amphibious operations in the South Pacific. Langley and Winkelstein report 16 per 1,000 from an American Evacuation Hospital in Northern France. The cases of perfringens infection which form the material for this paper represent 15 per 1,000 of the battle casualties admitted to a general hospital behind the North Burma front. As will be indicated presently, only one-half of these were true gas gangrene. An analysis of the incidence of gas gangrene in these battle casualty cases, therefore, using the criteria quoted from the Surgeon General's report on World War I, is 6 per 1,000 in wounds involving soft tissues only, and 17 per 1,000 for those with associated compound fracture.

A brief note of the type of work done in this hospital will be helpful in the interpretation of what follows. Situated from 75 to 200 air miles behind an advancing front, the casualties from both American and Chinese ground forces were received by air evacuation. Combat occurred in jungle terrain with heavy soil contamination because of poor hygiene among natives and Chinese troops. The wounded were transported by litter bearers to a portable surgical hospital, set up close to the fighting front and adjacent to a rice paddy or other cleared area where liaison planes of the Piper Cub type could land and evacuate the wounded to larger fields accommodating transport (C-47) planes. From this point there was a one to two hours' flight and a seven-mile ambulance trip to this hospital. Despite the difficulties, evacuation was accomplished with extraordinary rapidity. The average time elapsed between wounding and admission to this general hospital was approximately two days. For the most part, the evacuation hospitals played no part in this chain of evacuation. Often, as might be expected, the tactical situation, lack of landing strips for planes, or extraordinarily thick weather caused delays in air evacuation. The importance of early surgical débridement is emphasized strikingly by the fact that the most severe cases in the entire series occurred in one combat unit which for ten days was cut off from any surgical care other than the limited facilities of their own battalion aid station. It is of some interest to note in passing that the etiologic factor of spore contamination of woolen clothing did not exist, since only cotton was worn in the jungle.

In this report has been included every patient admitted to the hospital over a two-year period who exhibited clinical manifestations of infection by the anaerobic gas-forming organisms. The clinical diagnosis was supported by bacteriologic findings in every case. It should be emphasized that, in approximately one-half the cases under consideration, infection was confined to the region immediately adjacent to the wound, and therefore these cases were not true gas gangrene. Cases have not been included in which clostridia were an incidental finding, but only those with clinical manifestations of acute infection. Had laboratory facilities permitted routine culturing of all wounds, there is no doubt that many more would have been found to harbor these ubiquitous organisms. For example, they were found in an abscess about a shell fragment in the lung and on several occasions about foreign bodies in the brain. There

was no indication in these cases that the presence of clostridia was of clinical significance despite the recent Russian report which indicates that they may, in certain instances, produce serious and even fatal encephalitis. No pathogenic gas-forming anaerobes other than those of the *Clostridium welchii* group were encountered.

CONTRIBUTING ETIOLOGIC FACTORS

The factor of greatest importance in influencing the course of the infection seems to be the integrity of the principal arterial trunk of the injured extremity. When this is intact, the infection can be expected to remain localized. However, when there is damage to the brachial or femoral arteries or to both branches below their bifurcation, gas gangrene will probably supervene. The bearing of this observation upon prognosis and surgical management will be discussed presently. It is indeed surprising that in the past attention has been concentrated upon the infectious aspects of the condition to the neglect of this vascular element. It would be thought that the term gangrene alone would have preserved a proper focus. The Surgeon General's *United States History of the World War* does so, and this report contains one of the best descriptions of the pathology of gas gangrene which has ever appeared and is a source of information on the subject which has been too generally overlooked. It states, in effect, that anaerobic bacteria are incapable of producing gas gangrene by their presence alone and must be accompanied by, first, the failure of circulation; second, extensive cellular damage to large quantities of muscle under conditions that prevent free access of oxygen; and third, a constantly progressive increase of this series of factors. These conditions are fulfilled only when there has been damage to a major arterial channel. In thirty-two cases of gas gangrene of an extremity, dissection of the amputated limb disclosed injury to the main arterial trunk in sixteen. In nine additional patients who had had amputations prior to admission, the field record indicated that severe vascular injury was responsible for their gas gangrene. Had the amputated limbs of the seven patients remaining been carefully dissected, we are confident that vascular injury would have been found. Thus, in the gas gangrene cases, certainly 72 per cent, and probably 100 per cent, had major vascular damage. The thirty-seven patients in whom infection remained localized to the region of the wound provide a contrast in that only three (8 per cent) had vascular damage, and this was limited in its extent. One had embolism of the popliteal and two had severance of the anterior tibial artery alone. The course of the disease is so altered by a background of major arterial damage that this feature would seem a more rational basis for classification than the currently popular use of the terms anaerobic cellulitis and anaerobic myositis which are misleading as well as inaccurate. Cellulitis suggests diffuse infection of the superficial tissue planes, whereas it is well recognized that the layer of devitalized muscle is the favored medium for the proliferation of the clostridial anaerobic. Practically speaking, therefore, all cases of clostridial infection can be described as myositis, but the integrity of the circulation of the part is of far greater significance than the depth of the involvement.

The usual arterial damage in battle casualties is a laceration, severance or thrombosis of the vessel due to the missile itself or its explosive force in the tissues. Excessive tension within the tissues may also produce an inadequate circulation. Thus, the compression of a swollen limb by a snug-fitting plaster cast may cut off circulation. The same effect may be obtained by increasing edema within an unyielding muscle sheath, or by progression of a confined hematoma. In civilian practice the factor of arteriosclerosis, either senile or diabetic, must be given consideration.

The influence of soil contamination has already been noted, but these organisms are so ubiquitous that soil is only one of many sources of infection. It was of some interest to note that during the first nine months that this hospital was in operation, not a single case of clostridial infection was observed among a large number of patients treated for crushing injuries and compound fractures resulting from vehicular injuries. During this period, the hospital was serving American supply and Chinese combat troops in training. Later, when the same troops moved into Burma, these infections appeared with regularity. This cannot be explained except on a basis of poorer sanitary conditions in the forward areas. Nor can the fact be explained, except perhaps on the basis of an acquired racial immunity, that the incidence of clostridial infection in American casualties was twice that in Chinese casualties. All except five of the cases considered were associated with battle wounds. Of the exceptions, three occurred in injuries sustained in truck or tractor accidents; one was in a knife wound with severance of the anterior tibial artery, incurred while cutting bamboo; and one was the result of a TNT explosion with extensive thromboses. There were associated compound fractures in thirty-two (46 per cent) of the sixty-nine cases observed. Extensive necrotized soft tissue was noted in most cases, indicating that the débridement had been incomplete, but there was an occasional exception to this rule.

DIAGNOSIS

In any serious wound, careful investigation should be made into the adequacy of the arterial circulation. The history of the injury and its location are often more significant than abnormal physical findings. Any evidence indicating that a main arterial trunk may be damaged should put the surgeon on the alert to watch hourly for the onset of gangrene and to act accordingly. This was learned by sad experience when three patients in whom vascular damage had not been suspected developed gangrene in the wards. Several precious hours were lost before amputation and these patients died. Two other patients presented an extensive and hopeless gas gangrene on admission and it was obvious upon reviewing the records that arterial injury was present, but its significance was overlooked by previous attendants. There were, on the other hand, eleven patients whose circulation was recognized as being in a precarious state upon admission. These were all watched very closely and recovery in each instance followed amputation performed at the first evidence of gangrene.

It should rarely be difficult to detect clostridial infection if the surgeon is alert to its possibility. The first four days after injury are the critical ones and

the diagnosis was made within this period in 75 per cent of the cases. A careful direct examination of the wound seldom leaves any doubt in the mind of the experienced surgeon concerning the presence of an anaerobic gas-forming infection. The pulse and temperature chart cannot be relied upon. The laboratory affords methods of bacterial confirmation by smear, but time cannot be lost in awaiting the results of cultures. Sudden increase in pain in the wounded part is a warning signal which requires careful inspection of the wound. As the dressings are removed, the diagnosis may frequently be made by the detection of a "dead house" odor. It is characteristic and unmistakable and is more readily observed at a slight distance than by sniffing directly over the wound. In the early stages, marked edema, tension in the tissues, and a thin serosanguineous discharge may be the only visible signs. Later, crepitation is present in the tissues and also a mottling of the skin with bleb formation. The depths of the wound reveal discolored necrotic muscle, and gas escapes as sealed cavities or tissue planes are opened. Subcutaneous emphysema may be encountered sometimes in wounds of the chest wall or neck, where atmospheric air is trapped under the skin. This should not lead to a mistaken diagnosis, since the typical signs of a clostridial infection are absent from these cases.

No other infection progresses as rapidly as a fulminating case of gas gangrene. It may advance perceptibly in the course of one-half hour. The earliest case in this series was one in which the diagnosis was made twelve hours after the injury and the soldier was dead eighteen hours later. On the other hand, infection may smolder in a wound for days and suddenly light up. One such patient was under careful observation because he had gangrene although no apparent infection of the foot. Refrigeration therapy was tried during this period, in the hope of avoiding above-knee amputation, but on the twenty-second day gas was detected and thigh amputation was necessary. Experience with refrigeration was very limited due to lack of ice, but no effects were observed from it other than the dubious benefit of delaying the onset of clostridial infections.

Delays in the recognition of gas gangrene occurred in all the echelons through which these patients passed. The record is far from perfect. The first case encountered developed in the wards of this hospital. The wound was concealed by a thoracobrachial cast and suspicions of the seriousness of the condition were further dulled by the fact that an associated malarial fever was brought under control by atabrin. It was customary for the patients to arrive encased in plaster casts and there were one or two experiences of this sort of discovering clostridial infection unexpectedly at the removal of the cast. Therefore, an invariable rule was made that the cast must be removed immediately upon admission whenever there was a history which suggested injury to a main artery, whenever there was any evidence whatsoever of circulatory embarrassment, or whenever there was the slightest suspicion that clostridial infection might exist. Continued surveillance of such cases is essential to avoid disaster. On one occasion a nurse on duty at night reported that one of the patients was experiencing unusually severe pain in the wound and that the toes appeared to be dusky. The ward officer had inspected this wound just before he retired and the sig-

nificance of these observations did not impress him. Seven hours later gangrene had extended to the thigh and, although amputation was done, it did not avert a fatality. It is, of course, easier to be wise in retrospect than to be consistent in making the right decision at the time. However, honest criticism of results is good for the soul and helpful in the future. A review of the records of thirty-two cases of gas gangrene leads to the conclusion that, had the diagnosis been as prompt and the surgery as adequate as it might have been, the mortality rate could have been reduced from its actual level of 31.3 per cent to a figure in the vicinity of 20 per cent.

SURGERY IN GANGRENE

No delay can be countenanced in resorting to appropriate surgery as soon as a surgeon is satisfied that he is dealing with clostridial gangrene. Appropriate surgery implies amputation. An extremity which is gangrenous is dead and cannot be salvaged. It beclouds the issue to talk of resecting muscle groups. The cases wherein such a limited procedure has been successful were not true gas gangrene within my concept of the term. They were localized clostridial infections. A patient with true clostridial gangrene cannot be made a better risk for operation by resuscitative or supportive measures. These are needed but should be carried out coincidentally with the operation rather than in preparation for it. A patient with gas gangrene does not improve while waiting for the surgeon's knife and not one has been saved without amputation. There are a few patients who seem to be beyond hope of salvage, but even in an apparently moribund patient the desperate gamble which major amputation often involves should be taken. This seemingly radical viewpoint is the product of experience during the early stages of which three patients were regarded as too advanced for radical surgery. Multiple incisions were made in one of these and the other two were not operated upon at all. All three continued relentlessly to a fatal termination within a few hours. Subsequently, recovery followed prompt amputation in at least two patients whose condition on admission appeared to be equally hopeless. The futility of expecting improvement under preoperative supportive measures was driven home by another experience. A patient seriously ill with gas gangrene was given a transfusion and developed a severe reaction. The operation was accordingly postponed and intensive supportive therapy instituted. The gangrene and the toxemia progressed relentlessly. As a last resort amputation was performed after thirty-six hours, but by that time the patient's scant chances for survival had been sacrificed.

Amputations for gas gangrene should be done at a level with good blood supply. This will not coincide with the upper limits of crepitation in the tissues nor even with the furthermost extent of infection. Recovery has been witnessed after amputation below the shoulder even though subcutaneous emphysema had infiltrated the pectoral region. Patients have been seen repeatedly who did well despite the persistence for many days after amputation of crepitation and of infection in the stump. These cases can be satisfactorily managed as localized clostridial infections provided the circulation of the part is adequate. A limited

experience with hip and shoulder joint disarticulations has not shown that they have any advantages to compensate for the additional operative shock involved and the additional tissue planes which they lay open to infection. The three requirements of amputation in clostridial gangrene are that it be done through a level which ensures vascularity, that it be of the stepped-guillotine type, and that it be left wide open without sutures. In this series of thirty-two patients with gas gangrene, three had no amputation, ten had amputations at the portable surgical units, and nineteen had operations performed in this hospital.

SURGERY IN LOCALIZED INFECTION

In the cases where the infection is localized and there is an adequate circulation in the extremity as a whole, it is not necessary to sacrifice the limb. There is not the same desperate urgency about immediate operation as there is for gangrene, but nevertheless there should not be undue delay. My experience included thirty-seven of these cases, none of which progressed to gangrene. Thirty-six of the cases involved an extremity and all patients recovered without loss of the limb. The one case which terminated fatally was a clostridial infection which involved the abdominal wall too extensively for surgical excision. Death from toxemia resulted within twelve hours of this soldier's admission to hospital. In these wounds the organisms proliferate and infection disseminates throughout devitalized tissue under anaerobic conditions. The rationale of surgical intervention is to modify these conditions by the excision of necrotic tissue and the exposure of closed cavities to the air. It is not always possible to remove all the dead tissue at the time of operation and some of the excision may be left for secondary dressings, but it is important that all fascial planes be laid open so that no sealed-off pockets remain. The subsequent dressings of these wounds are major surgical procedures which must be carried out at least once a day. All necrotic tissue must be trimmed away painstakingly until clean granulations cover the surfaces. During this period the oxidizing agents such as zinc peroxide, hydrogen peroxide, chlorazene, and potassium permanganate all have a useful function in supplementing by chemical means the basic objectives of the surgical wound excision. Somewhat later after the slough has been separated, local application of penicillin seems to be helpful in preparing the surface for skin grafting or suture.

ADJUNCTS TO OPERATION

The replacement by transfusion of blood loss which occurred at the time of original injury and during operation is urgently needed in all cases. It constitutes a most important aspect of treatment. Plasma is of value in restoring depleted proteins, but is not a substitute for whole blood in these patients. All will require large amounts of blood on the operating table and during the early postoperative period. The war has taught us to think in terms of gallons rather than pints of blood. This obvious need for transfusion strictly as replacement therapy renders academic any discussion of its value in combating toxemia, although its advantage from this standpoint may also be argued. It has never been shown conclusively that the sulfonamide drugs possess specific affinity

against the clostridial organisms in man. However, the infection of these wounds is invariably a mixed one and among the secondary invaders sulfonamide-sensitive streptococci are common and become important after the clostridial infection has burned itself out. Accordingly, it is sound therapy to institute sulfonamide therapy early in order to build up an effective blood level at a period when it becomes essential.

Experience with the use of perfringens antitoxin had been very limited prior to the war. Some of us cherished the belief that greater benefit might have been apparent had it been administered in larger dosage than customarily. Consequently, in the earlier cases the available supply of antitoxin was drawn upon liberally for the American patients, giving usually 13,000 units every six hours. There were thirteen patients who received a total dosage of 100,000 units or more, with a maximum dosage of 208,000 units. Since the antitoxin was not available for administration to Chinese patients, there was a parallel series of controls. Midway in the series stock was taken and it was impossible to discover that any advantage had accrued from the use of antitoxin. Thereafter, antitoxin was given only to an occasional patient and, in reviewing the series carefully, no reason could be found to regret this deliberate omission.

Enthusiastic reports have appeared concerning the value of penicillin in the therapy of these cases, particularly its prophylactic benefit when given in large dosage in the forward installations soon after wounding and before definitive surgery could be done. I agree with Cutler and Sandusky and with Jeffrey and Thompson that it must be considered only as an adjunct to early and adequate surgical intervention, although the experience does not provide data for a sound assessment of its value. In the early phases of the Burma campaign, penicillin was not available and it was during this period that most of the cases of frank gas gangrene were encountered. Later, when the drug was available in liberal amounts, evacuation of the wounded from the front had been accelerated, earlier errors in the use of constricting plaster casts had been corrected, and there was an alertness to the possibilities of clostridial infection throughout all echelons. A considerable number of cases were seen of localized clostridial infection during this period, but, as has been shown, this group has virtually no inherent mortality risk, and relative morbidity is difficult to prove statistically. Thus we have recourse only to personal impressions of the benefit accruing in six patients with true gas gangrene. One of these had had amputation before admission and died within twelve hours. A second had amputation as soon as gangrene was detected on the third day after injury. He received one-half million units of penicillin without appreciable effect upon the downhill course. The other four patients recovered but in three of them this might have been predicted because the presence of gas gangrene was recognized and amputation done within forty-eight hours of wounding. In the final case, the patient was admitted four days after receiving the wound. He had had several incomplete débridements in the forward hospital and the gangrenous thigh was amputated promptly upon admission to this hospital. Postoperatively he received two million units of penicillin and this may well have been a factor in determin-

ing the outcome. It is, however, the only case of gas gangrene in which penicillin appeared to have had significant influence.

Of the group which localized clostridial infections, twenty patients received penicillin in total dosages varying from 600,000 up to five million units. No penicillin was given in seventeen cases which, therefore, represent a comparable control group. None of these localized cases progressed to gangrene and all had the same type of conservative surgery. There were no observable differences in the course of the penicillin-treated cases from that of the controls except for its obvious value in controlling infection due to associated organisms.

SUMMARY AND CONCLUSIONS

1. Experience with the treatment of clostridial wound infections occurring among Chinese and American troops in North Burma emphasizes the importance of differentiating between those with major vascular damage and those without such injury.

2. Gas gangrene is unlikely to develop unless the integrity of the main arterial blood supply is impaired either by the initial trauma or, secondarily, by such factors as tension within closed tissue compartments or external constriction by improperly applied plaster casts.

3. There were in this series thirty-two cases of true gas gangrene, representing an incidence among combat wounded of seven cases per 1,000 casualties. The mortality in this group was 31.3 per cent, and there were none who survived without a major amputation. Neither delay in resorting to surgery nor conservatism in its performance can be countenanced in dealing with this condition. A stepped-guillotine amputation through a level of good blood supply without suture of the stump constitutes the indicated surgery.

4. The cases of wound infection by clostridial organisms in which the main blood supply of the part remains intact present an entirely different problem and a much more favorable prognosis. In thirty-seven such patients, none developed gas gangrene, none required amputation, and only one (with an extensive involvement of the abdominal wall) died. Limited surgical excisions which eliminate anaerobic conditions from the wound are adequate for this type of case.

5. All other measures are subordinate to timely and adequate surgery. Blood replacement therapy by massive transfusions is imperative. The sulfonamide drugs are useful although probably not specific. The use of perfringens antitoxin has proved disappointing in practice. Our data do not provide a good basis for evaluating penicillin in these infections, but its use as an adjunct to surgery is advocated.

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PENICILLIN IN TREATMENT OF CRANIOCEREBRAL INJURIES OF WAR

With Particular Reference to Its Intraventricular Use

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THE high incidence of infections consequent to open (compound) craniocerebral and spinal injuries of war has demanded the use of every therapeutic agent and technique known to medical science. In World War II the Army Medical Department made available all of these agents and in particular it has been the good fortune of the Medical Corps to have large supplies of the newest of these, penicillin, in forward installations where definitive care could also be rendered to the injured soldier. It has been my opportunity to study the action of penicillin in more than 250 cases of acute craniocerebral and spinal cord injuries. These patients were observed for the most part in evacuation hospitals, and a few were seen in general hospitals, in the Southwest Pacific Theater of Operations. The details of these experiences have been recorded elsewhere.[1]

Because of the comparative innocuousness of penicillin sodium, together with its apparent great prophylactic and therapeutic efficacy in treatment of intracranial wounds, I wish here to record briefly a few observations on the use of this antibiotic agent in sixty-two cases of severe open (compound) craniocerebral injuries. Particular mention will be made of the intraventricular application of penicillin, emphasizing its prophylactic value and the absence of toxic or irritative reactions even when it is used in large doses.

One of my first experiences with penicillin sodium in treatment of cranial injuries came with the successful treatment of a soldier who had severe pneumococcic (type XXXII) meningitis subsequent to a basal cranial fracture.[2] The observations made on this patient and on subsequent patients whose meningitis was treated intracisternally and intrathecally with penicillin disclosed that the inflamed leptomeninges, and probably the ventricles also, tolerate heavy concentrations of penicillin in the cerebrospinal fluid. When untoward effects did occur they were mild and transitory, as was noted in the foregoing case, in which 100,000 units of penicillin sodium were introduced into the basilar cistern.† It was, therefore, planned to administer penicillin routinely by the intracranial (intracerebral, intraventricular, intracisternal, or intrathecal) route in all cases of craniocerebral injuries in the ensuing Philippine campaigns in which I participated.

MATERIAL

Observations were made on the use of penicillin in more than 200 cases of acute cranial injuries of all types. In this group there were sixty-two cases of

Received for publication, April 10, 1946.

*Now returned to civilian status, Rochester, Minn.

†The untoward effects consisted of nausea, headache, increased respiration, slowing of the pulse, and a temperature of 103° F.

severe open (compound) craniocerebral wounds in which operative intervention was performed and penicillin was administered locally. In all of these cases there were contusions and lacerations of the brain consequent to indriven bone, metallic fragments, or bullets. In nineteen instances either bony fragments, metallic fragments, or both had entered or perforated one or more ventricles.

The Medical Corps was fortunate in the Philippine campaigns to receive the patients who had cranial wounds at evacuation hospitals within a relatively short time following injury, usually within two to twelve hours, but occasionally as late as three days. These patients had received only minimal treatment in the forward echelons, consisting of a field dressing, plasma, and occasionally also morphine tartrate. Seldom had ill-advised surgical treatment been attempted.

PLAN OF TREATMENT

All patients who had cranial injuries were admitted directly from the incoming ambulances to the "shock tent," where their first examinations and treatment were begun. The routine treatment consisted of 2 units of double strength plasma,* followed by 100 c.c. of a 5 per cent solution of sulfadiazine sodium and 50,000 units of penicillin sodium (dissolved in 10 c.c. of isotonic saline solution), all given intravenously. Frequently it was necessary to administer from 500 to 1,500 c.c. of whole blood because of the acute loss of blood consequent to the craniocerebral injury or other wounds. As soon as the patient's condition would permit surgical intervention, he was taken to the operating room and surgical treatment was instituted.

Operation was performed with the patient under one of three types of anesthesia: local (infiltration with procaine hydrochloride and block anesthesia), combined local and intravenous anesthesia (pentothal sodium), or ether-oxygen anesthesia (intratracheal, closed type).

Penicillin was placed intracranially in all wounds according to the following plan. If the brain was lacerated so that a ventricle was found to have been exposed or the foreign body entering the brain had traversed the ventricle, then 25,000 to 50,000 units of penicillin sodium dissolved in 5 c.c. of isotonic saline solution were introduced into the affected ventricle at the time it was surgically explored. If, however, a small missile had perforated a ventricle and lodged elsewhere and the damage in the cerebral tissue consequent to this was so small that open (visual) exploration of the ventricle was not considered advisable because of the increased trauma incurred by such operative intervention, then penicillin was injected into the ventricle through a ventricular cannula or a small catheter introduced along the track of the missile. Other deep cerebral wounds received 50,000 units of penicillin dissolved in 5 c.c. of isotonic saline solution directed into the wound, while more superficial wounds received a similar amount placed underneath the dura after its closure had been accomplished.†

Penicillin was also used in the scalp wound to irrigate the wound (250 units per cubic centimeter) and also after débridement and closure of the scalp

*Two units of plasma dissolved in 250 c.c. of isotonic saline solution.

†In all instances the dura mater was closed, either by primary suture or with fascial grafts (temporal or fascia lata). Fibrin film was not available.

(10,000 units). Powdered penicillin (crystals) was occasionally sprinkled on uncovered areas of epicranium when there was excessive loss of scalp tissue but was not used as such intracranially. As the calcium salt of penicillin was not available I have not had any experience with its intracranial use such as has been reported by Cairns and his associates.[3]

I was not favorably impressed by the results of my earlier intracranial use of sulfonamides; hence, local sulfonamide therapy was not used in this series of craniocerebral injuries.

The postoperative treatment included either oral or intravenous administration of sulfadiazine, in sufficient doses to maintain a concentration of 10 to 15 mg. per 100 c.c. of blood and parenteral administration of penicillin. The latter was given intramuscularly in doses of 25,000 units every three hours as routine therapy. This treatment was continued for five to seven days. A few patients received from one to four intracisternal (cisterna magna) injections of 25,000 to 50,000 units of penicillin sodium in 5 c.c. of isotonic saline solution each; no patient received more than one injection a day.

CLINICAL OBSERVATIONS

It was not possible to follow these patients for a period sufficient to warrant the drawing of any definite conclusions about the incidence of infection and therapeutic efficacy of penicillin, for they were observed only from five to seventeen days in the evacuation hospitals. However, follow-up reports were received from many of them as late as three months after injury and personal follow-up was continued on a few to general hospitals; they were thus observed for thirty to sixty days. So far as I was able to determine there were no postoperative intracranial infections in any of these sixty-two cases. One patient, however, a Filipino boy, whose wound was eighteen hours old at the time he received definitive treatment, did have an infection of the scalp after two weeks. This was traceable to improper handling of the wound after he was transferred to a civilian hospital.

The anesthetists and I observed all of these patients closely at the time when penicillin was introduced into the brain. Particular attention was given to those who received penicillin by the intraventricular route. These observations failed to reveal any untoward effects following the local injection of penicillin into the brain, ventricles, and intracranial subarachnoid spaces at the time of the operation or subsequent thereto. Particular attention was paid to the pulse, respirations, blood pressure, occurrence of vomiting, and condition of the skin. If the patient was conscious, his state of consciousness was closely observed. At no time could we detect any evidence of a toxic or irritative reaction which could be attributed to the penicillin.

The innocuous nature of penicillin was forcefully brought to attention in one case wherein operation was performed with the patient under local anesthesia. This soldier was semiconscious throughout the operation, which necessitated the removal from the left lateral ventricle of a small fragment of bone consequent to a shell fragment wound. Although 50,000 units of penicillin in 5 c.c. of isotonic saline solution were introduced into the exposed ventricle and

later 25,000 units of penicillin were placed beneath the dura mater after it had been successfully closed there were no untoward effects. The pulse, blood pressure, respirations, state of consciousness, and condition of the skin remained unchanged. The postoperative course was uneventful, the temperature did not rise above 100.4° F., and his state of consciousness steadily improved. The maximal pleocytosis was 210 cells per cubic millimeter of cerebrospinal fluid (by lumbar puncture). In this case there was no penicillin introduced postoperatively into the cisterna magna or lumbar subarachnoid space. The scalp wound healed quickly by primary intention.

No toxic or irritative reactions were discerned in the other cases in which penicillin was administered by intraventricular method at the time of operation nor was there evidence of intracranial infection during the brief period in which the patients were observed. One patient, a young Filipino boy whose condition was poor at the time of operation, was observed to show an increase of pulse rate of about 15 per minute after 30,000 units of penicillin (in 5 c.c. of solution) had been placed into the left lateral and third ventricles; his general condition was not otherwise altered. He had an uneventful postoperative course save for a delayed infection of a scalp wound.

Penicillin was used locally in seven cases of compound (open) injuries of the frontal lobe which were complicated by extensive fractures of one or both cribriform plates and by similar involvement of the frontal or other accessory nasal sinuses. All of these patients were operated upon within fourteen hours of their injury. The wounds were explored through unilateral or bilateral transfrontal craniotomy with débridement of the brain and closure of the dura mater. In certain instances the closure of the dura mater necessitated the use of fascial transplants. Penicillin (50,000 units) was placed into the cerebral wounds and additional penicillin (25,000 units) was injected extradurally after closure of the scalp. There were no untoward symptoms in any one of the seven patients thus treated. All were observed for at least thirty days and at that time there was no evidence of infection or of leakage of cerebrospinal fluid in any of them. The wounds healed by primary intention.

Among the group who received penicillin by intracisternal methods (25,000 to 50,000 units) in the postoperative period only three complained of headache, nausea, and vomiting. In all of these cases there were a slight decrease of the pulse rate and an elevation of the respiratory rate. All symptoms were transitory except for headache, which persisted from one to four hours. The cell count of the cerebrospinal fluid did not disclose evidence of meningeal irritation from the penicillin for there was a steady decrease of the cell count, although none of the patients had had more than 1,000 cells per cubic millimeter at any time.

GENERAL CONSIDERATIONS

Minor toxic or irritative symptoms consequent to intracisternal, intraventricular, and intrathecal routes of administering penicillin have been recorded by Rammelkamp and Keefer[4] in 1943, Cairns and his associates in 1944,[3] and others.[2, 5] In 1942, Florey and Jennings[6] showed experimentally that toxicity

decreases with increasing purity of penicillin. Cairns and his associates stated that "with intrathecal injections few reactions have so far been encountered and these also show variations depending presumably on particular impurities present in different batches." These workers also expressed the opinion that there may be serious damage in injecting large doses of penicillin into the ventricles because of reactions. More recently Johnson and Walker[7] have reported untoward effects following the introduction of 50,000 units of penicillin into the ventricles of a patient suffering from postoperative meningitis. This reaction was characterized by loss of consciousness and clonic seizures of the extremities with subsequent recovery. However, as has already been pointed out, Vogel and I[2] injected 100,000 units of penicillin into the cisterna magna in a single dose with only moderate and transitory reaction characterized by increased respirations, decreased pulse rate, mild fever, and headache. These symptoms were not alarming and could be avoided or minimized by decreasing the dose to 50,000 units or less. Furthermore, in this and other patients observed by us there was no evidence that penicillin increased the pleocytosis in the cerebrospinal fluid, for the cell count decreased coincidentally with the clinical improvement. Since the patient had shown a reaction to the intravenous injection of penicillin it was suggested that the reaction may have been due to impurities in the penicillin.* It is also possible that these symptoms were due to a mild idiosyncrasy to penicillin. The observations made in the series of cases reported here lend credence to the suggestion of the presence of impurities in the penicillin.

Cairns and his associates observed a slightly different group of symptoms after ventricular injection of either sodium or calcium penicillin (250 or 500 units per cubic centimeter). "It consisted of patchy erythema of the skin of the trunk and limbs, often coming and going, generalized sweating, intermittent goose skin, slight rise of pulse rate and sometimes vomiting, the whole passing off in ten to twenty minutes." These observers attributed these symptoms to impurities in the solution and not to the penicillin, a conclusion which seems to be correct in the light of further observations. However, in two cases of meningitis not included in the series reported here, vomiting occurred following the intracisterna administration of 50,000 units of penicillin. This reaction was followed by moderately severe headache, which lasted about three to four hours. Decreasing the dose to 10,000 units did not alter the reaction in either case. These two are the only reactions of this type which I have encountered.

The observations herein recorded are entirely in accord with those recorded earlier by Florey and Florey,[8] Fleming,[9] Florey and Cairns,[10, 11] Keefer and his associates,[12] Evans,[13] Lyons,[14] Herrell, Heilman, and Williams,[15] and others.[3-5, 16-18] However, none of these investigators have used as large amounts of penicillin in single doses as I have described here and elsewhere.† Pilcher

*The penicillin received was frequently yellow orange or bright orange. A few patients who were given intramuscular and intravenous injections of penicillin made from these ampules of penicillin had febrile reactions with cutaneous reactions like those reported by Cairns and his associates.

†Since this was written the intracisternal injection of similar large doses of penicillin has been reported by Neymann, Heilbrunn, and Youmans,[19] by Weickhardt,[20] and by others, with conflicting evidences of irritability and toxicity.

and Meacham[5] presumed from their experiments on dogs that the "transitory meningeal reactions are roughly proportional to the dose" of penicillin. Although this has not proved to be entirely correct it can be shown that in most of the cases in which there is a reaction to such large doses the symptoms may be diminished or avoided by a reduction of subsequent doses.

Several investigators[2, 3, 9, 13] have shown that pleocytosis consequent to the inflammation of the meninges (in meningitis) decreases coincidentally to the recovery from the infection, thus strongly suggesting the lack of irritative effect of the penicillin. It is of interest, however, that the introduction of 10,000 units of penicillin into the subarachnoid space of normal persons produces remarkable pleocytosis.[4] Why the inflamed leptomeninges tolerate penicillin better than the normal meninges has so far not been explained. In view of these findings it was somewhat surprising to note the lack of a clinically demonstrable toxic or irritative reaction to penicillin introduced into the ventricles in cases of acute craniocerebral injuries. Here again one is led to suspect the presence of impurities in the penicillin used by those reporting these reactions. It would be of interest to repeat these studies now that a more highly purified product is available.*

The necessity of using such large doses of penicillin as have been described here and elsewhere may justifiably be open to question and criticism. Rammelkamp and Keefer,[4] Keefer and his associates,[12] and others,[6, 8] have advocated the use of smaller doses, that is, 10,000 units or less[10, 11] given intrathecally once or twice a day. According to reports this dose seems to be adequate in the majority of cases.

However, it also has been shown that there is a hazard of penicillin fastness[25-27] in certain bacteria and that this must dictate the intensiveness and effectiveness of the initial dose for all infections, particularly for staphylococci, streptococci, and pneumococci. Without laboratory control of the potency of penicillin as well as the bacterial susceptibility one cannot be certain what is the optimal or adequate dose in any given case. Certainly this is the situation with which the neurosurgeon is confronted when working, as he must, under field conditions, treating severely contaminated craniocerebral injuries and meningitis. One must consider all these craniocerebral wounds as grossly contaminated and in those cases in which patients receive the first definitive care after twenty-four hours one must consider the wounds as undoubtedly infected. It furthermore has been pointed out that the "proteolytic clostridia recovered

*Since this paper was submitted for publication a considerable amount of literature has accumulated on the subarachnoid and intraventricular use of penicillin. From the work of Walker and his associates[21, 22] it would appear that there is grave danger in the intraventricular, intracisternal, and intrathecal injection of penicillin; particularly is this true in using larger amounts of the antibiotic agent. Their work has been corroborated by others (Miller[23]; Reynolds and Moore [24]). However, some investigators have not encountered these severe reactions (convulsions, coma, death, or even less severe reactions of fever, muscular twitchings, paralysis, pleocytosis in the cerebrospinal fluid, and so forth). From a review of these more recent contributions it would seem preferable to start penicillin therapy with smaller doses and gradually increase the concentration. It also has become evident that there are patients who are sensitive to pure crystalline penicillin. Thus, the matter of impurities in penicillin as a cause for reactions seems to have been fairly well ruled out. Such reactions, however, appear to occur very infrequently and from my experiences and those of others in using penicillin deep in craniocerebral wounds (including the ventricles) I am not convinced that the risk of adverse reactions is great enough to outweigh the dangers of severe intracranial infections. Although the evidence presented here does not prove that patients with penetrating craniocerebral wounds are less likely to react unfavorably to penicillin, it may be that this is true.

from war wounds require four to five times as much penicillin as do Staphylococci."[14] Therefore, in view of the probability of the presence of proteolytic clostridia and of resistant strains of bacteria in craniocerebral injuries, as well as in traumatic meningitis and cerebral abscess, I believe that it is entirely justifiable to use the larger doses of penicillin. This is all the more true now that it has been shown that the untoward effects either are absent or, if present, are minimal and transitory.

SUMMARY

Clinical observations are detailed on the local application of large doses of penicillin in acute craniocerebral war wounds. In a series of more than 200 cases of cranial injury studied in the Southwest Pacific Theater of Operations, sixty-two patients had severe open (compound) craniocerebral injuries and all of these received penicillin into the intracranial wounds. Included in this group were nineteen cases in which one or more cerebral ventricles had been exposed or perforated by metallic fragments, bullets, or edged weapons (bayonets). Penicillin was placed into the ventricles of each of these patients in doses of 25,000 to 50,000 units. In no instance were untoward toxic or irritative reactions observed. In one case 100,000 units of penicillin were placed in the cisterna magna in the treatment of pneumococcic meningitis. Only transitory and mild untoward symptoms resulted and the patient recovered.

In view of the known contamination of war wounds with proteolytic clostridia and of the presence of resistant strains of bacteria which require many times as much penicillin as do other strains (susceptible strains), it is considered justifiable to use large doses of penicillin such as has been described in this report.

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WAR WOUNDS OF THE CHEST

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THE early evacuation of casualties makes it difficult for the surgeon in an active theater of war to follow his cases for an adequate length of time. At a general hospital, however, it was possible to observe for a period of approximately three months or until their return to duty, or final disposition, 106 patients with war wounds of the chest. These were German prisoners of war who had been treated initially in hospitals near the front according to the established procedures of today. The common complications, the method of handling these complications, and the results are presented here.

It is necessary, first, to distinguish between simple penetrating wounds of the chest such as those produced by rifle bullets or other sharp missiles and massive wounds such as those caused by shell fragments. The simple penetrating wound, the type commonly seen in civil life, causes a minimal disturbance of the cardiorespiratory system. Treated by the so-called closed method, a large number of these patients will recover without subsequent surgery. In military practice, however, the second type is more common and many will require later operative procedures since convalescence is associated with a variety of complications. In the massive wounds of the chest, disturbance of physiology is of paramount importance and it is essential to repair the damaged viscera and close securely the thoracic cavity in order that the cardiorespiratory system may function adequately. It should be noted, however, that, depending on its course, a small missile may seriously damage a vital organ. Frequently with shrapnel wounds there is an associated blast injury which produces further disturbance in the cardiorespiratory mechanism and the late complications of recurrent hemothorax. Hemothorax may result in dense fibrous pleuritis around the lung, with a collapse of the lung which must be corrected.

Chest wounds are of greater importance because serious complications are more commonly encountered here than in any other part of the body. The initial treatment is of great importance but the follow-up and continued observation require much consideration as sequelae should not be minimized. The associated trauma to other parts of the body further complicates the treatment of chest wounds but the initial therapy should be directed toward the thorax before treatment of other injuries is undertaken.

The shock encountered in chest wounds is usually out of proportion to that of wounds elsewhere. For purposes of classification, the shock in these cases may be divided into that due to hemorrhage and that due to disturbance in the cardiorespiratory mechanism. The usual evidences of shock, such as lowering of the blood pressure and decreased cardiac output, and the concentration of the red cells, are not at first demonstrated in individuals with penetrating wounds of the chest. This may be because, with the suddenness and

Received for publication, April 10, 1946.

TABLE I. WOUNDS OF CHEST

Total cases	106
Mortality	.9%
Total infection	22.6%
Empyema	20.7%
Returned to duty within 120 days or less	72.5%

severity of the shock, insufficient time is allowed to manifest all of the changes after the injury. In other words, following the massive trauma, the shock is critical or the damage done is not irreparable. The hemorrhage encountered is of variable degree and type. In civil cases the hemorrhage present is more often of the controllable type, that is, a moderate nonprogressive, internal blood loss, which ceases without operative procedure, unless vital organs are involved. Bleeding directly from the parenchyma of the lung usually ceases spontaneously. In the uncontrollable type, such as bleeding from an internal mammary or intercostal artery or from a larger vessel in the thorax, the shock is progressive and fails to respond to the usual method of restoration. It is particularly important in these cases to operate as early as possible in spite of the presence of shock. However, attempts at replacing blood and maintaining circulatory volume should always be made. Intrathoracic hemorrhage may mechanically interfere with the function of the heart and the aeration of the other lung.

Intrapericardial bleeding produces marked symptoms from a small blood loss: if, from a small penetration of the pericardium, the blood collects within the sac, cardiac tamponade results, this is manifested by distant cardiac sounds, apparent increase in the size of the heart, lowering of the cardiac output, and distention of the veins of the neck, evidence of an increase in venous pressure. This condition is an urgent emergency and must be corrected immediately if the patient is to survive the pressure of the blood within the pericardium. On the other hand, if the wound in the pericardium is very large and there is no wound of the heart muscle, evidences of the tamponade cannot be demonstrated. The blood, instead of distending the pericardial sac, accumulates in the pleura.

There are many manifestations of disturbed cardiorespiratory mechanism. The production of an open pneumothorax is the most common of all these disturbances; positive pressure is produced within the thoracic cavity by the entrance of atmospheric air: air is brought into the chest on inspiration and expelled with expiration, that is, a so-called sucking wound results. This positive pressure is exerted on the large vessels and decreases the amount of blood entering the heart. The lungs may become partially deflated and inadequate oxygen exchange occurs. The immediate closure of these openings is essential if the effects are to be minimized. The amount of shock varies directly with the size of the opening in the thorax.

The development of a tension pneumothorax may be manifested immediately after the trauma or it may be exhibited several hours or days after the injury. These conditions are produced by a flap tear in the lung which acts as a trap and allows the entrance of air from the lung into the pleural cavity without the opportunity of escape. The increasing pressure within the thorax must be

recognized and relieved at the earliest possible moment. Any abnormal variation of thoracic pressure on the two sides may be a contributing factor. Combined abdominal and thoracic wounds may cause further disturbance of the function of the chest by creating a positive pressure on one or both sides. Injuries to the diaphragm as such or injuries to the innervation of the diaphragm may produce a paralysis of the muscle which results in the paradoxical motions. Acute manifestations of this add to the increasing shock associated with these wounds. Cardiac tamponade, as already noted, may contribute to the disturbance of cardiorespiratory mechanism.

It is essential to determine the degree of shock and the ability to relieve it before undertaking any surgical procedure. In those in whom hemorrhage is uncontrollable, operation may be undertaken immediately; however, a certain number may be safely handled after the patient has completely responded to the immediate treatment. In many instances it is impossible to estimate the extensiveness of a lesion until operation. However, determination can be made and the proper procedure outlined as soon as satisfactory examinations, including x-ray, have been completed.

A group of 106 patients, treated in a general hospital, are being reported in detail. The mortality was 0.9 per cent. Since all these patients were German prisoners of war, many had had a delay in the initial forward treatment, varying from twelve to forty-eight hours, due to the exigencies of battle. It is noted that the percentage of infection was high, 22.6 per cent. Empyema accounted for 20.7 per cent, and infection of the lung or of the chest wall for the remainder. This percentage is unusually high; it may be partially explained by the delay in the initial treatment. However, chemotherapy, instituted in all cases, minimized the severity of these infections and permitted earlier surgical procedures, thus producing more complete recovery. The results obtained were reflected in the percentage of patients (72.5 per cent) returned to duty in 120 days or less. Of the remaining 27.5 per cent the chest wound was not the only factor preventing their return to duty. Injury to the spinal cord or brachial plexus, fractured femurs, and, in one instance, acute psychosis were some of the associated problems. The initial treatment in each of these cases was the same as if performed routinely in the care of the American battle casualty.

The treatment in the forward hospitals may be divided into the following categories: first, resuscitation; second, closure of sucking wounds; and third, the débridement of the damaged structures to the chest wall and the underlying viscera.

TABLE II. ORIGINAL OPERATIVE PROCEDURES

Débridement and closure of sucking wounds		68
Thoracotomy		38
Repair of diaphragm	9	
Suture of lung	7	
Splenectomy	6	
Drainage of liver	6	
Removal foreign body of lung	2	
Nephrectomy	1	
Suture of Stomach	1	

TABLE III. SECONDARY OPERATIONS

Decortications	16
Drainage of empyema	14
Drainage of subphrenic abscess	5
Drainage of lung abscess	2
Removal foreign body of lung	2
Repair of diaphragmatic hernia	1
Total	40

Resuscitation is accomplished by the administration of whole blood in quantities sufficient to restore the loss and to correct the existing shock. The first 500 c.c. can be administered at the normal rate but all subsequent transfusions must be given slowly in order not to overload the already damaged respiratory mechanism. Early aspiration of the tracheobronchial tree, either with a catheter or by means of bronchoscope, will aid considerably in diminishing the difficulty of breathing. Oxygen, of course, may be beneficial at this time to decrease the hypoxia while preparing the patient for a definite operative procedure.

Closure of the sucking wounds may be accomplished satisfactorily by the application of tight pressure dressings which can be held in place until a more definitive closure is accomplished. Many a penetrating wound becomes a sucking wound as soon as débridement is undertaken. With small wounds of entrance there frequently may be a large wound through the intercostal spaces that perhaps may be sealed by the muscles on the posterior and lateroposterior chest wall. Débridement must be done carefully removing all skin, damaged muscle, and loose rib fragments. Closure of the pleura is not easy, but the use of the intercostal muscles and pleura and the accessory muscles of the chest wall when closed in layers will satisfactorily effect a closure of the thoracic cavity. It is most essential to close all of the layers on the anterior chest wall because so frequently a disruption of the chest wall will occur due to its normal respiration motion. Wounds have been seen to disrupt and develop an open pneumothorax in one week to ten days after the original closure of the anterior pleura and the intercostal muscle, when the accessory muscles and skin were not effectively closed.

Intercostal nerve blocks relieve the patient of the immediate pain and allow for a more complete respiratory effort, early coughing, and the removal of retained blood and secretions from the bronchi. In the open thoracotomies, the procedure can be accomplished easily by the injection of 1 per cent procaine in the intercostal spaces from within. In those in whom an open thoracotomy was not performed, an injection of two to three intercostal spaces above and below the levels of the wounds of entrance and exit is advisable. This procedure can be repeated daily depending on the symptoms.

In order to prevent late complications it is essential to aspirate as nearly as possible all retained blood and air. At the time of the initial treatment the chest should be rendered as free of blood and air as is possible. In so many instances the blood becomes organized and compresses the lung, resulting in atelectasis. In the collapsed lung serious impairment of function occurs and there is a likelihood of prolonged disability. The presence of blood predisposes

to infection and frequently massive empyema develops. The intramuscular administration of penicillin in 25,000 unit doses every three hours is routine. At the time of aspiration 40,000 units may be injected into the pleural cavity and repeated with each subsequent aspiration. However, penicillin cannot be satisfactorily employed intrapleurally when drainage tubes are in use; to clamp the tube will result in the development of a blood clot obliterating the lumen, thus destroying its usefulness as a drain.

It is most important that the use of drains be made with due consideration of their purpose and a knowledge of their benefit and at the same time with regard to their dangers. When a forward thoracotomy is done a larger tube should be brought out at the dependent portion and attached to an underwater seal. The purpose of this tube is to allow removal of the accumulated blood and at the same time to maintain continued expansion of the lung. This tube will function as a drain from twenty-four to forty-eight hours, after which time either the lung becomes fixed or the tube becomes plugged with clotted blood. This state is noted by a cessation of the oscillations of the water column. The tube should be removed at this time because if allowed to remain in for a longer period, the likelihood of infection will be increased. The insertion of a small anterior drain in the second intercostal space will further decompress the accumulated air and prevent the formation of a tension pneumothorax if damage to the underlying lung exists. This tube also should be removed at the earliest moment to prevent infection.

An analysis of the initial treatment of those patients is interesting in that in 68 the initial treatment was that of simple débridement and a closure of the sucking wounds when they existed. An open thoracotomy was performed in 38 cases for various reasons; it was necessary to repair the diaphragm in 9 instances, to suture the lung in 7 instances, and to remove the spleen in 6 instances. Drainage of the liver was done by the subdiaphragmatic route in 6 cases. Foreign body was removed from the lung in only 2 cases. The stomach was sutured through the transdiaphragmatic opening in 1 instance. This analysis does not separate those cases that were directly associated with the wound in the chest. There has been much discussion in regard to the advisability of a formal exploration of the thoracic cavity as the primary treatment. This procedure carries with it a certain danger and perhaps allows for more frequent complications than are probable in patients in whom thoracotomy was not done. Aside from the fact that these patients usually are not in good condition to withstand long operative procedure, it is believed that most corrective surgery could best be withheld until the patient's chances for making complete recovery are greatest. The usual indications for forward thoracotomy are the presence of an increasing uncontrollable intrathoracic hemorrhage, the complete débridement of the pleura where rib fragments and foreign material are present and the transdiaphragmatic wounds in order to explore this region for possible damage to viscera both above and below the diaphragm. The presence of a small metallic foreign body as such is not necessarily a reason for early thoracotomy. In suspected damage of the pericardium or the mediastinal structures, immediate explorations are governed by the symptoms presented, namely, those of cardiac

TABLE IV. COMPLICATIONS

38 Early Thoracotomies	
Empyema	9
Constricting pleuritis	7
Bronchial fistula	5
Lung abscess	2
Subphrenic abscess	2
Tension pneumothorax	1
68 Conservatively Treated Patients	
Empyema	13
Constricting pleuritis	7
Bronchial fistula	6
Subphrenic abscess	3
Lung abscess	1

TABLE V. AVERAGE PERIOD OF HOSPITALIZATION

Hemopneumothoraces	62 days
Decorticated cases	52 days
Empyemas (decorticated)	58 days
Empyemas (open drainage)	100 days

tamponade or other associated disturbances of the cardiorespiratory mechanism. An analysis of the complications of the forward thoracotomies compared with those not receiving a forward thoracotomy were similar.

There were thirty-eight cases of early operation; empyema developed in nine, bronchial fistula in five, subphrenic abscess in two, a chromic fibrous pleurisy with associated atelectasis in seven, and tension pneumothorax in one case.

The complications of the 68 conservatively treated patients were as follows: Empyema developed in 13, lung abscess in 1, bronchial fistula in 6, subphrenic abscess in 3, chronic fibrous pleurisy with atelectasis in 7. This comparison indicates that there is not a great deal of difference in the number of complications.

It is interesting to note that of the 106 patients, 78 had repeated aspirations. The average number of aspirations per case was 3+. The average blood removed in any one case was 6,350 c.c. (this patient developed a total empyema necessitating decortication). The greatest number of aspirations in one case was 20; empyema developing on both sides was corrected by rib resection with recovery. It is noted that if the first aspiration yields a greater amount of blood and subsequent aspirations decrease in amount, the prognosis is generally good. However, this does not always hold true because organization of the clot may prevent aspiration. Continued refilling in spite of aspiration is significant in that organization is continuously taking place and the likelihood of expanding the lung compressed for a long time is not good. If the fluid increases in amount, it will probably be necessary to perform decortication.

In spite of excellent care in the forward hospitals, there are many necessary procedures which are essential for the purpose of shortening the convalescence and also of preparing those patients in whom late operations are indicated. The most essential problem is that of improving the patient's general condition as

much as possible before undertaking any operative procedure. In most instances where the hematocrit and total red count indicate a rather marked anemia, the blood should be returned to its normal levels by repeated transfusions. It is still necessary to give blood with much precaution during this period, as in the beginning. Many patients require as much as 1,500 to 2,000 c.c. of blood before the hematocrit is raised to 45 volumes per cent. The administration of proteins and vitamins is of much importance. Aspirations should be continued in those patients who continue to show evidence of either fluid or air. Many of these patients can avoid secondary operations if this effort is continued at this stage. Within two to three weeks after injury one is able to estimate the most likely outcome. It is felt that the injection of air following aspirations should not be done because it further delays expansion.

Penicillin is administered routinely in all patients who show evidence of sepsis but it is felt that such therapy alone will not substitute for adequate removal of infected blood in the pleura or an infection within the lung. The persistence of hemopneumothorax alone is not an indication for either penicillin or the sulfanilamides. These should not be given routinely over a long period of time. Particularly is this true in individuals in whom a residual amount of blood remains in the pleura without evidence of sepsis. Before and after removal of foreign bodies, penicillin is administered as a prophylaxis and lessens the likelihood of reinfection of what dormant infection might have been present. If there is a low-grade infection following aspiration, penicillin may be instilled into the pleural cavity with beneficial results. When the lung has been fixed and further expansion seems impossible, the prolonged intrapleural injection of penicillin is not indicated. It is well to evaluate each case and to withhold penicillin unless there are definite indications.

Of the 106 cases, it was necessary in the fixed hospital to perform major operative procedures in 40. There were 16 cases of decortication, 14 of drainage of empyema, 5 of subphrenic abscess, 2 of lung abscess, and 2 of foreign bodies of the lung; 1 diaphragmatic hernia was repaired. It is necessary, therefore, that many of these patients be prepared as quickly as possible to increase their chances for early surgery and also to lessen the chances for secondary operations. Within a period of four to six weeks after the injury, the outcome can be fairly well determined. That is, the chest has been aspirated dry and a residual hemothorax or diaphragmatic hernia can be detected, the necessity for removal of remaining foreign bodies can be determined, or the likelihood of septic process developing from hematomas or foreign bodies within the pleura or lung estimated. Taking into account the original thoracotomies performed in a forward hospital and those performed in the general hospital, a total of 27 major procedures were performed in the 106 cases. This number apparently is somewhat large but it is felt that, because of the type of wounds encountered and also the time lag before the initial treatment, this number is in keeping with the general experience of others.

The results obtained in chest wounds are perhaps over-all as good as those obtained in any group of war injuries. If the patient survives the immediate effect of trauma and has had adequate treatment, both in the forward and rear

hospitals, the chances for survival and return to duty are excellent. This statement is supported by the fact that 72.5 per cent of the patients were able to do either full duty or some type of limited assignment within a 120 day period. The period of hospitalization varies with the type of injuries. In all patients with hemopneumothorax the average period of hospitalization was sixty-two days. This includes both the uncomplicated cases and cases complicated by empyema or atelectasis. In those patients requiring decortication, the average hospital stay was fifty-two days, the shortest period for the entire group. In the group of patients developing empyema and on whom an early decortication was performed, the average period of hospitalization was fifty-eight days. All patients with empyema, regardless of the method of treatment, remained in the hospitals for an average of ninety-three days. Those patients who were treated by rib resection and drainage remained in the hospital for an average of 100 days. It is obvious, therefore, from these figures which take into account only those patients who were returned to duty, that patients in whom an early decortication is done will have a lessened period of hospitalization.

COMMENT

As already mentioned and as has been emphasized by many, there is a marked difference between civil and war thoracic injuries. Not only is the manner of production different but the factors concerned are likewise variable. Heretofore, conservative handling of chest wounds has been met with fairly satisfactory results, that is, the avoidance of operative procedures except when indications for surgery are definite. This principle still has its merit and should be utilized when treating simple penetrating wounds of the chest.

Considerable experience during World War II has shown that the morbidity can be shortened and a more complete recovery accomplished by early decortication of lung expansion. This is always important, but particularly so in the wounded soldier. The maintenance of fighting strength and the return to an early useful occupation are the greatest concerns.

It is not always necessary to resort to operative means for the correction of a collapsed lung. Early and repeated aspirations of blood and air from the chest often accomplish this end. Unfortunately, in a great number of cases the attempts at removal after a few days are not successful because of clotting of blood and organization. If the lung is fairly well expanded and there remains only a small amount of material, absorption will occur in time, provided infection does not develop.

On the other hand, when the lungs remain completely collapsed for several weeks and with the development of thick fibrous pleurisy, the tendency for this to be permanent is great as time elapses. It is most necessary then that early removal of this fibrous constriction be done before the parenchymal changes become permanent and infection takes place.

Decortication or the removal of the fibrous constriction from the visceral pleura should be performed early to speed recovery as well as to accomplish the procedure before organization and fixation develop further to increase the technical difficulties.

The procedure of decortication is not a new one but has been popularized and widely used in early restoration of the function of the lung. It must be borne in mind constantly that many residual accumulations of blood do not require radical procedures. The indications are well established and must be adhered to if the greatest benefit of the procedure is maintained.

The use of the sulfanilamides, and particularly of intrapleural and intramuscular penicillin, has made possible decortication for early traumatic empyema. Without the benefit of penicillin the procedure is not without danger of spread of infection both locally and generalized. The problem in each case arises as to when empyema should be drained and when decortication should be performed. It is felt that a localized and well walled-off empyema will recover about as rapidly by simple drainage as by more radical means. It is still to be remembered in the presence of thick localized pus that the treatment to afford complete drainage is adequate surgery. The utilization and institution of those surgical principles will bring about such an end. The affordance of sufficient drainage at the most dependent portion of the cavity and the maintenance of the drainage are very important.

The early traumatic infected hemothorax can be treated successfully by decortication. This is best exemplified in those cases in which the lung has been to a great extent collapsed. If this condition is treated by repeated aspirations, either with or without penicillin, expansion of the lung cannot occur. Moreover, the pus will usually become thickened and open drainage must be instituted. The lung cannot then expand due to this fibrous peel and in many instances the empyema will become chronic, requiring many months for recovery. Early decortication of the totally collapsed lung with an infected hemothorax has definitely decreased the mortality and heretofore prolonged disability.

Rehabilitation of patients with war wounds of the chest depends first upon the mechanical correction of the deranged cardiorespiratory system through surgical procedures. However, respiration can be accomplished more quickly and more efficiently by a systematic program of rehabilitation. This should begin soon after the man has been wounded and should be continued throughout his stay in the hospital. At first perhaps he can utilize only the accessory muscles of respiration to expand the lung, but free motions of the arms and shoulders is begun as soon as possible and he is gotten out of bed early. The physiology of respiration is explained to each patient and with the aid of a large mirror he is taught to expand the upper or lower part of either side. He is also taught to place his hand over the effected part so to feel the expansion. In this program all chest patients are grouped together and a spirit of competition arises, both individually and collectively, which speeds recovery. An intelligent convalescent patient with the gift of leadership, under the supervision of the medical officer and with the aid of the ward attendants, is the ideal leader for these specialized exercises. It is felt that with improvements in our surgical knowledge and with the rehabilitation program painstakingly carried out, the morbidity of chest wounds has been lessened and earlier recovery effected.

CEEPRYN AS AN ANTISEPTIC FOR THE PREOPERATIVE PREPARATION OF THE SKIN

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IT IS the experience of most surgeons that the standard skin antiseptics which are in use in good hospitals are satisfactory in that if the skin is thoroughly scrubbed with soap and water and then shaved, washed again with clear water, then with 70 per cent alcohol, then with ether, and after drying is painted with one of the skin antiseptics in general use, an operation can be performed with relative safety in so far as infection from the surface of the skin is concerned.

On the other hand it is recognized that the methods of preoperative skin preparation in general use do not render the skin bacteriologically sterile. Recent evidence on this point is furnished by the work of Ives and Hirshfeld.[1] From swabs of skin which had been prepared by washing several times with soap and water, then with 70 per cent alcohol, and then painting with several coats of kalmerid (1 per cent potassium mercuric iodide in 85 per cent acetone and 15 per cent water), Ives and Hirshfeld were able to grow bacteria in 86 per cent of the cases in which the skin was swabbed before the operation. When they swabbed the skin at the end of the operation, positive cultures were obtained in 100 per cent of the cases and all of these latter containing staphylococci. They stated that "any improvement in surgical technique which will decrease the contamination of operative wounds by bacteria from the air of the operating room or the skin of the patient should result in a decrease in the incidence of postoperative wound infection." This incidence of postoperative wound infection was stated to be 5 per cent.

Lovell[2] has shown that even if the surface of the skin could be satisfactorily sterilized by mechanical and chemical methods, many bacteria, chiefly staphylococci, remain in the hair follicles where they cannot be reached by any of the methods of skin sterilization now in use. The surgically sterile fragments of skin were excised during the operations, placed in culture media, and incubated. They were then fixed, sectioned, and stained after the bacteria had multiplied to a point where they could be identified with ease.

Lee and Hoxworth[3] compared merthiolate and an isotonic aqueous iodine solution as skin antiseptics and concluded that they are of about equal value. When fragments of skin which had been prepared with these solutions were cultured, positive cultures were obtained from 20.7 per cent of those painted with merthiolate and from 29.7 per cent of those painted with iodine.

The introduction of Ceepryn led to the hope that possibly because of its combined antiseptic and detergent action it might penetrate more deeply into the hair follicles and not only sterilize the surface of the skin, but also kill the

Received for publication, May 22, 1946.

bacteria which were located in the hair follicles. If this were found to be true it would indicate that ceepryn is considerably more efficient than any of the other skin antiseptics now in common use.

Ceepryn (cetylpyridinium chloride) is a cationic detergent quarternary amnonium compound. Its surface action is responsible for its penetrating power in tissues and into the bacterial cell wall. Blubaugh and associates[4,5] demonstrated in vitro that ceepryn is bactericidal against a wide variety of pathogenic gram-positive and gram-negative microorganisms, both in the presence and in the absence of organic matter (10 per cent serum). Sarber,[6] in in vivo studies of various antiseptics, found ceepryn to have the highest relative efficiency as to penetration and activity in the presence of living tissue. Green and Birkeland[7,8] demonstrated that ceepryn and other cationic detergents were superior to mercurials, halogens, and phenol in experimental infections of the chorioallantoic membrane of the chick embryo, in reducing the degree of infection without tissue damage.

The skin antiseptics which have been used most frequently are tinctures of merthiolate 1-1000, mercresin 1-1000, and 3½ per cent tincture of iodine. They have been used indiscriminately as one seems to be about as efficient as either of the others. Iodine is objectionable in that some patients are sensitive to iodine and develop skin irritation after its application. This may be a serious post-operative complication, especially when the field is large and the part is immobilized in a plaster cast. In my experience neither merthiolate nor mercresin has caused skin reaction, but both are slightly objectionable because of the stain which is difficult to remove. In order to compare these with ceepryn, the method of culturing skin fragments was used because of special interest was the effect of the antiseptics on the bacteria in the hair follicles.

The routine method of skin preparation is as follows: The patient enters the hospital the day before the operation and the operative field is scrubbed with soap and water, shaved, washed again, and then washed with 70 per cent alcohol. Usually the skin is washed with alcohol and ether on the operating table before the antiseptic is applied, but occasionally this is omitted. We abandoned the forty-eight hour skin preparation and the preliminary covering of the operative field with a sterile dressing several years ago and have not regretted the change to the simpler procedure as the results seem to be better.

In testing ceepryn and the other antiseptics, one-half of the operative field was painted with tincture of ceepryn 1-1000 and the other half with another anitseptic, the line of division being approximately at the middle of the proposed skin incision. When the skin incision was made a thin sliver of skin was excised from the margin of the skin on either side of this line. This sample was about one inch long and quite thin, but included the entire thickness of the skin. An attempt was made to make the samples uniform in size, because it is obvious that if bacteria are present in the skin the number of positive cultures obtained will vary directly with the size of the skin fragments which are cultured. The excision of these fragments did not interfere with the closure or healing of the wounds and a postoperative infection developed in only one of the wounds in this series.

The two skin fragments from each incision were folded in sterile sponges moistened with normal salt solution and sent to the laboratory for culture in the routine manner. Each fragment was planted in a flask of plain beef broth and examined in from forty-eight to sixty hours.

The results of the cultures of the skin fragments excised from 248 clean operative incisions at the start of the operations and submitted to the laboratory for routine culture are shown in Table I. In this table the upper six lines

TABLE I. RESULTS OF CULTURES OF EXCISED SKIN FRAGMENTS AFTER PREPARATION OF THE SKIN WITH VARIOUS SKIN ANTISEPTICS

ANTISEPTIC USED	NUMBER OF CASES	POSITIVE CULTURES	PER CENT POSITIVE	POSITIVE FOR STAPHYLOCOCCI	PER CENT POSITIVE FOR STAPHYLOCOCCI
Ceepryn	50	14	28	8	16
Merthiolate	50	21	42	16	32
Ceepryn	50	10	20	10	20
Mercresin	50	10	20	8	16
Ceepryn	50	8	16	8	16
Iodine	50	4	8	4	8
Ceepryn	14	2	14	2	7
Phemerol	14	2	14	2	14
Iodine	14	4	28	2	14
Scrubbed with Ceepryn	56	17	30	9	16

represent cultures from split skin preparations in which one side of the field was prepared with tincture of ceepryn 1-1000 and the other side with tincture of merthiolate, mercresin, or iodine, and a skin fragment was excised from each side. The incidence of positive cultures was highest in the series with ceepryn and merthiolate and lowest in the series with ceepryn and iodine. It is probable that part of this lowered incidence of positive cultures is due to improved technique in handling the specimens with a lessening of contamination from outisde. In the small series of forty-two wounds in which ceepryn, phemerol, and iodine were each used in fourteen wounds without splitting the skin preparation between two antiseptics, positive cultures were obtained from the excised skin fragments as follows: ceepryn, two; phemerol, two; and iodine, four. It is thus evident that there is not much difference in the efficiency of the various antiseptics tested and the figure of 34, or 20 per cent, positive cultures (twenty-seven, or 16 per cent, staphylococci) from 164 wounds in which the skin was painted with ceepryn is about what could be obtained by this method in a large series with any of the standard skin antiseptics. If larger fragments of skin are used for culture this figure can be increased.

In order to determine whether or not the detergent action of ceepryn would result in more effective sterilization of the skin, a series of fifty-six cases was cultured in which the skin of the operative field was washed with alcohol and ether and then scrubbed for two minutes with sterile gauze and tincture of ceepryn 1-1000. In this group seventeen (30 per cent) of the cultures were positive and nine (16 per cent) of these contained staphylococci. It is thus evident that in this experiment, scrubbing of the skin for two minutes with tinc-

ture of ceepryn did not sterilize the skin more effectively than did the usual method of painting the skin with the antiseptic.

This failure to increase the efficiency of the skin sterilization by scrubbing with the antiseptic is at variance with the results obtained by Helmsworth and Hoxworth.[9] These authors obtained positive cultures from 58.2 per cent of the cases when the skin was painted with 1-1000 tincture of ceepryn and from 37.7 per cent when it was painted with 1-500 tincture of ceepryn. But when the skin was scrubbed for five minutes with a 1-100 aqueous solution, positive cultures were obtained from 10.3 per cent of the skin fragments and after a ten-minute scrub with the 1 per cent aqueous solution the percentage of positive cultures was reduced to 5.4 per cent. It is thus evident that prolonged scrubbing of the skin with a 1-100 aqueous solution of ceepryn is more effective than painting or a short two-minute scrubbing with the tincture of ceepryn 1-1000.

Staphylococci were the predominant organisms in these cases and appeared in 68, or 17 per cent, of 398 cultures; 63 of these were *Staphylococcus albus* and 5 were *Staphylococcus aureus.* In two instances diptheroids also grew in the cultures which contained *Staphylococcus albus.* In the remaining twenty-four positive cultures, the organisms identified were hay bacilli, nine; *Bacillus subtilis,* five; diphtheroids, five; *Streptococcus viridans,* one; M. sarcinae, one; *Micrococcus tetragenus,* one; *M. catarrhalis,* one; and moulds, one. Some of these especially the hay bacilli, were undoubtedly contaminants.

From observation as reported in this paper and from experience in using it, tincture of ceepryn 1-1000 is an efficient and satisfactory antiseptic for the preoperative preparation of the skin. No ill effects have been noted from its use for this purpose in several hundred patients and its stain can be removed with relative ease with soap and water. It does not, however, completely sterilize the skin, nor does any other skin antiseptic with which we are familiar. The bacteria, mostly *Staphylococcus albus,* which are embedded deep in the hair follicles are not killed by the antiseptic which is applied on the surface, and observations indicate that scrubbing of the skin for two minutes with the tincture of ceepryn 1-1000 does not increase the efficiency of the skin sterilization.

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Recent Advances in Surgery

Conducted by Alfred Blalock, M.D.

HYPERPARATHYROIDISM

A Review of Historical Developments and the Present State of Knowledge on the Subject

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HISTORICAL REMARKS

THE study of the problem of hyperparathyroidism and its treatment by parathyroidectomy falls into three stages: (1) The advances made in the study of osteofibrotic affections of the bones; (2) The recognition of an anatomic relationship between the parathyroids and their tumors, on the one hand, and certain diseases of the osseous system, on the other; and (3) the closer insight gained into the relations existing between the parathyroids and the calcium metabolism.

A synthesis of results achieved in these different fields of research, although with different speed, led to the first successful parathyroidectomy in a case of Recklinghausen's disease in which a parathyroid tumor could be removed (Mandl, 1926). Since, as it appeared, the patient recovered completely, a number of problems involved seemed to be solved—a fact that was of greatest importance for practical surgery.

But, to return to the development outlined, only the third point is of particular interest for this study.

There can be no doubt that Erdheim (1906) was the first to recognize the relationship between the parathyroid glands and the calcium metabolism, rather than other authors often mentioned in the literature. Since his studies were later, in a positive as well as negative respect, of greatest importance for the development of parathyroid surgery they shall be dealt with in detail. It shall be seen later how great their importance is even today although Erdheim's theory, as far as it concerned the treatment of hyperparathyroidism, could be disproved.

Erdheim's fundamental experiments on rats consisting in extirpation as well as homotransplantation of parathyroid tissue very definitely revealed certain skeletal changes in the experimental animals. To begin with, after parathyroidectomy they consisted in defects of the enamel of the teeth, but later also in changes involving the entire skeleton. This was a fact from which Erdheim drew his well-known conclusions.

MacCallum and Voegtlin later, in 1909, established a definite relationship with the calcium metabolism, parathyroidectomy being followed invariably by lowering of the calcium level of the blood. They were able further to demonstrate that after the operation the quantities of calcium eliminated in the urine were increased and this condition was referred to as calcium diabetes.

These findings were verified by a number of other authors who did not add, however, substantially to the knowledge on the subject.

It is generally known that Collip's great discovery (1925),* the isolation of the parathormone, marked a turning point in the therapy of tetany. It further furnished the basis for many experiments which greatly improved the knowledge on the pathologic conditions in question. The experimental production in animals of a state to a certain extent coinciding with that of hyperparathyroidism was considerably facilitated by the use of Collip's parathormone in its various modifications (Jaffe, Bodansky and Blair, Johnson and Wilder, Mandl and Uebelhör and others).

Now there remains only the question of how parathyroid tumors or enlargement, when it was chanced upon during autopsy, was explained around 1925. No distinction was made by the majority of authors between the different malacias of the bone system and, following Erdheim's theory, the enlargement of the parathyroid glands was regarded as the consequence rather than the cause of the skeletal changes.

It was Erdheim who pointed out that the disturbance of the calcium metabolism preceded the enlargement of the parathyroids and increased gradually only to subside after rickets (the disorder with which Erdheim was preponderantly concerned) was cured. The parathyroids produce the secretion essential for the calcification of bones which in the malacias is used pathologically. Rickets, therefore, would be characterized by an intensified requirement of functioning parathyroid substance; the hyperplasia or hypertrophy of the glands would, therefore, constitute a compensatory reaction destined to cope with the additional strain placed upon the organs; parathyroid enlargement might, therefore, be paralleled to compensatory hypertrophy in general.

This theory of Erdheim which was approved by other authors was also applied to Recklinghausen's disease.

In treating patients suffering from this disease my first thought was to support the gland in its task of controlling the calcium metabolism by administering a potent parathyroid extract to the organism. My idea was that, should this procedure prove a failure, that fact would indicate (contrary to Erdheim's theory) that the new growth found in the parathyroid was to be considered the primary factor therefore, that nothing but removal of the parathyroid tumor would be effective in setting the disturbed calcium metabolism in order again and curing the disease.

CASE REPORT

A patient with disturbed calcium metabolism was admitted to department in October, 1924. Treatment with Collip's parathormone was tried, but with absolutely no result, none of the symptoms improving.

In July, 1925, four parathyroid glands, taken from another patient admitted to the hospital in a moribund condition, were implanted into the abdominal wall. None of the symptoms disappeared; the calcium content of the urine remained unchanged.

On July 30, 1925, a parathyroid tumor (measuring 25 by 15 by 12 mm.) was removed from the left inferior area behind the thyroid gland. On microscopic examination this was diagnosed as an adenoma.

*Editorial comment: It is only fair to state that Dr. A. M. Hanson should be credited with the independent discovery of the parathyroid hormone.

As early as a few days after the operation, the patient's condition began to improve. The calcium content of the urine and the calcium level of the blood were considerably lower. The patient felt better. No symptoms of tetany appeared. As early as four months later, roentgenograms showed denser lime shadows of the bones than before operation. The severe pain of the bones previously present also subsided. For the first time in years the patient was able to sit up in bed and to walk about on crutches.

The patient was readmitted to the hospital* in February, 1926, because of renal calculi and severe arthrosis of the knee joint. Continuous roentgen control, however, revealed improvement of the skeletal symptoms. The general condition was also good and the calcium metabolism normal. In view of a certain amount of doubt expressed by a number of authors in the literature concerning the significance of the operative procedure, the patient was watched very carefully and exact determinations were made of the calcium and phosphorus proportion in the blood and urine. The renal disturbance subsided after conservative treatment and the patient was discharged soon after.

At that time the patient's sister developed osteitis fibrosa localisata of the tibia which gave rise to spontaneous fracture of the bone. This osteitis fibrosa localisata (not Paget's disease) later resulted in the growth of a sarcoma which made it necessary to amputate the leg.

In the patient with morbus Recklinghausen, however, the lime content of the skeletal system continuously increased as time went on, so much so that it was thought that the case might not present morbus Recklinghausen at all but Paget's osseous disease.† This view was opposed vigorously‡ on the theory that it may have been that the skeletal system with its severe lime deficiency accumulated, after the successful operation, such excessive amounts of calcium that the picture became strongly indicative of pseudo-Paget.§

After six years of improvement the patient's condition grew worse. By September, 1932, he once more had a renal calculus. There was hypercalcemia again, the phosphatase level of the blood was lowered, the bones once more became decalcified, and the patient was incapacitated.

With the thought that there would be another parathyroid tumor, the patient was operated upon again (Oct. 18, 1933). Since, however, none was found, neither in the entire neck region nor in the mediastinum, a large portion of the thyroid gland was removed with the intention of thus removing simultaneously an intrathyroidal adenoma should there be one. Actually, microscopic examination made clear that two parathyroid glands had been removed by this thyroidectomy. The one had been situated within the thyroid tissue, the other just touched the outer area. The former was more than normal size but there were no other pathologic findings.‖

It was significant that (1) after operation no tetany developed although the patient had been deprived of three of the thyroid glands. It was, therefore, obvious that somewhere in the organism there must have been a substantial amount of active parathyroid tissue; (2) although the parathyroid activity had been greatly reduced there was no improvement in condition and no change of the pathologic calcium metabolism. (Today we are well acquainted with the fact that removal of normal parathyroid tissue is not likely to influence this condition—a fact that supports the theory that the parathyroid tumor is the primary factor in creating the disturbance.)

No improvement was attained and the patient succumbed in February, 1936. Autopsy¶ did not reveal parathyroid tissue or a parathyroid tumor anywhere in the body although all sites where the misplaced organ could be expected to be present were carefully inspected.

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*The author reported this case in the Zentralblatt für Chirurgie (1926). However, it is described further here since in this patient, unfortunately, the process ran an unusual course, apart from the immediate postoperative improvement, which persisted for six years.

†Opinion expressed by Kienböck.

‡Mandl. Beitr. z. klin. Chir., 1934.

§In this the author has been supported by Snapper, Chifoliau and Braine, and others.

‖According to C. Sternberg's view.

¶The autopsy records with a number of photographs taken at every stage were unfortunately lost at the Institute in Vienna.

In later similar cases with the same immediate results and a rather similar clinical and chemical-pathologic aspect, the patients were operated upon and within a few years it was generally agreed upon that, as we call it now, "the osseous type of hyperparathyroidism" calls first of all for removal of a parathyroid adenoma. Publications on operations of this kind up to 1932 (see Lièvre, 1932) were made by Eiselsberg-Gold; Barr, Bulger and Dixon; Boyd, Milgram and Stearns; Eggers; Wilder; Snapper; Hunter; Barr and Bulger; Lièvre and Chifoliau; Compere; Pemberton and Geddie; Disque, Sainton, Bourguignon and Millot; Lièvre; Quick, Hundsberger and Schnabel; Hunter and Walton; Snapper and Boere. Clinically, the aspect offered by all these cases is rather uniform: in the majority of them the onset is with pain in the bones and extremities and great lassitude. There are further attacks of vomiting and occasionally the history contains reference to symptoms of the urogenital system. Polydipsia and polyuria are just as often mentioned as renal calculi which, however, and this should be particularly stressed, in the majority of cases have occurred a long time before and play no decisive role at all at the time when the patient is examined and the diagnosis made.

Extraordinarily frequently spontaneous fracture is reported as the first sign of the disease which is often the only reason for consulting a physician. Roentgenograms often reveal skeletal changes of the Recklinghausen type (cysts, brown tumors, softening of the skeleton characterized by deformation of the long tubular bones).

Other criteria of hyperparathyroidism are hypercalcemia, hypophosphatemia, hypercalciuria and hyperphosphaturia, increased phosphatase in the blood serum.

In case an encapsulated tumor is palpable in the neck region this is usually part of the thyroid gland since parathyroid tumors only rarely offer palpatory findings (see under technique of parathyroidectomy).

Where a parathyroid tumor could be removed operatively, it was particularly the negative calcium balance that was rapidly normalized. The calcium level of the blood soon dropped and the calcium elimination in the urine became less. Within six to twelve months the bones showed an increased calcium content and their structure gradually became normal. This fortunate development is not, however, encountered invariably.

DEVELOPMENTS AFTER 1932

Very probably, the synopsis of cases given previously includes only the successful ones. Very little is known about the proportion of failures and Churchill was presumably right when he said, "A brief period of confusion then followed during which surgical endeavours were controlled by neither pathological findings nor chemical data. In their eagerness to explore a new territory surgeons became incautious and floundered in a field beset with pitfalls and blind alleys."

Churchill and Cope, though, in 1934 reported eleven operations. In all of them an adenoma of one or two parathyroids was found which had to be considered the factor responsible for the derangement of the calcium and phos-

phorus metabolism, and normalization was invariably achieved after removal of the adenoma. Attention was also drawn by these authors to the abnormal localization of the parathyroid tumors to which I referred in 1933. Churchill and Cope (1934) emphasized the danger with which operation is fraught in the presence of an abnormal localization and advised surgeons to be careful not to remove normal parathyroid tissue should they be unable to detect a parathyroid adenoma.

The further development of parathyroid surgery as well as the study of hyperparathyroidism, as it were, lay in the hands of the staff of the Massachusetts General Hospital where by a teamwork of all departments new light was thrown on all problems involved.

Thus, in 1934, Albright, Bloomberg, Castleman, and Churchill were the first to draw attention to cases in which hyperparathyroidism was not, as it had up to then been the rule, associated with an adenoma of one or, although rarely, two parathyroids but that there existed a variety of hyperparathyroidism characterized by hypertrophy of the entire parathyroid tissue. Cases of two parathyroid adenomas had already been referred to by Hellström and also by Hunter but these novel findings had up to then been unknown. There was no adenoma but a general hyperplasia of the entire parathyroid tissue characterized histologically by "uniformity of the structure, the enormous size of the cells, and extreme clearness of the cytoplasm." On the strength of findings obtained in three cases these authors expressed the opinion that from that time on hyperplasia of the parathyroid glands with hyperparathyroidism should be regarded a disease entity. This seems justified particularly as clinically the three cases presented a number of similar features; the bone changes were completely overshadowed by the "renal type" of hyperparathyroidism.

Cope, of the same group of investigators, in 1935 reported upon twenty-seven operations for hyperparathyroidism. In this series the classical picture with one or maximally two adenomas occurred twenty-one times while the cases of "hyperparathyroidism associated with hyperplasia of the entire parathyroid tissue" had risen to six. Again, in the latter group, renal calculi governed the scene along with normal or nearly normal bone findings. The disturbance of the calcium-phosphorus metabolism is the same as in the classical type to become normalized after reduction of the parathyroid tissue.

In 1936 the number of cases reported by Churchill and Cope had risen to thirty. Ten of these cases were of the classical type, skeletal findings with or without renal complications predominating while eighteen were the renal type with or without association with osteoporosis.

The technique of reducing the diffusely hypertrophied parathyroid tissue is still being worked upon.

In 1944 Cope reviewed seventy-eight cases, a distinct majority of them the renal type. He, therefore, concluded that the renal complication of hyperparathyroidism is more common than osseous involvement. He further pointed out that any renal tract calcification brings suspicion of hyperparathyroidism and he emphasized the difficulty of distinguishing between primary and secondary hyperparathyroidism.

It is noteworthy that this novel type of hyperparathyroidism had up to then been found only by the Boston group. That this was not due to regional differences was shown by a report recently published from the Mayo Clinic by Keating and Cook. In the twenty-four patients operated upon with the diagnosis of hyperparathyroidism, the classical osseous type was the rarest, 66 per cent having bone changes and 92 per cent renal calculi as a predominant feature. For the diagnosis the decisive factor is the deranged calcium-phosphorus metabolism. In contrast to what had been reported by the Boston group, none of the twenty-four patients had the diffuse hypertrophy of parathyroid tissue as it had been reported there comparatively frequently, and all twenty-four patients had seasonal character is being studied (Ask-Upmark). Neither has the role of topography referred to.

THE CLINICAL PICTURE

A classification of the various types of hyperparathyroidism may be made from different viewpoints. According to the symptomatology, Shelling and also Kyser distinguished three groups of symptoms:

1. Symptoms due to hypercalcemia
   a. muscular weakness
   b. lassitude
   c. hypotonia
   d. chronic constipation
   e. occasionally slow pulse and cardiac arrhythmia (in severe cases tachycardia)
2. Symptoms related to the skeletal system
   a. pain of bones and joints
   b. cystic regions in the long bones and scalp
   c. spontaneous fractures
   d. kyphosis, scoliosis, and deformity of the thorax
   e. deformities of the long bones
   f. waddling gait or inability to walk
3. Symptoms due to transportation and excretion of calcium
   a. polyuria and polydipsia
   b. enuresis nocturna and dysuria
   c. renal complications

It shall be shown later that especially the renal symptoms have recently gained particular importance and often dominate the scene.

When describing the development of the disease we will have to deal with the most frequent type of hyperparathyroidism, that more or less progressively developing typical condition referred to by Lièvre as "forme typique evoloutive" covering the majority of cases of hyperparathyroidism.

However, in attempting a classification both pathogenesis and symptomatology should be taken into account.

PRIMARY HYPERPARATHYROIDISM

Let us, first of all, consider the type we should like to describe as primary hyperparathyroidism, falling into the following categories:

1. The classical osseous type caused by the presence of one or two parathyroid adenomas

2. The renal type caused by one or two adenomas
3. The gastrointestinal type (Morelle) caused by adenomas or hyperplasia
4. The type due to hypertrophy of the entire parathyroid tissue with osseous or renal complications with or without gastrointestinal symptoms.

Primary Osseous Hyperparathyroidism.—Usually primary osseous hyperparathyroidism progresses slowly. It is encountered more frequently in women than in men. According to Alexander and co-workers the average duration is three to nine years. In early youth up to the age of 10 years, it does not occur. It is most frequent between 30 and 60 years of age. Whether it is affected by regional or climatic differences cannot yet be decided with certainty and its seasonal character is being studied (Ask-Upmark). Neither has the role of dietetic factors yet been clarified. The first symptoms usually occur in the extremities, the pelvis, or spine and consist in pain in these parts. Spontaneous fractures or localized cysts or brown tumors, occasionally the first striking sign of the disease, lead the patient to a roentgenologist where a diagnosis is made. Very occasionally the x-ray diagnosis of hyperparathyroidism is made during a search for other symptoms. The roentgen signs of the disease are (a) generalized decalcification of the bones and (b) cysts or giant-cell tumors or a combination of both.

There exists no characteristic localization within the osseous system and the changes may occur anywhere. It is, indeed, an essential part of the roentgen diagnosis that there is no special localization but that large portions of the skeleton are involved. Usually the bone symptoms are not the only indication of the disease. There is almost invariable lassitude and weakness. Ask-Upmark (1938) drew attention to an accompanying rise of temperature. Vague gastrointestinal manifestations are common. After some time urogenital symptoms are likely to make their appearance and, unless some indication of them has already been made in the history, renal or ureteral colic may supervene.

Table I is a synopsis of the major symptoms recorded by Gutman in 150 cases of classical hyperparathyroidism.

TABLE I

	MAJOR INITIAL SYMPTOMS (PER CENT)	MAJOR LATE SYMPTOMS (PER CENT)
Skeletal		
Pain in the back or extremities	71	59
Muscular weakness	21	22
Pathologic fractures	27	36
Bone swelling	24	18
Gross deformities	17	35
Disturbances in gait	23	21
Bedfast	3	27
Renal		
Polyuria, polydipsia	9	12
Renal colic	9	4
Gastrointestinal		
Nausea, vomiting, anorexia	12	20
Epigastric pain	2	5
Marked weight loss	12	25

Biochemically the osseous type of primary hyperparathyroidism is usually quite well defined. Gutman reported, in the 91 out of 114 cases of hypercalcemia he published, distinct and even extreme values of over 12.0 mg. per 100 c.c. Only if, as it occurs in the late stages of the disease, renal insufficiency supervenes with retention of phosphates does the increase in the serum of calcium disappear. In cases of this kind it is of importance to determine the inorganic phosphorus and the nonprotein nitrogen in order to get a clear idea of the condition.

Since hypercalcemia is also encountered in other bone diseases (multiple myelomas, cancer metastasis), it cannot in itself be regarded a characteristic of hyperparathyroidism.

In the opinion of several authors hypophosphatemia is a reliable guide in the diagnosis of primary hyperparathyroidism. If it occurs together with hypercalcemia, the diagnosis is established. However, in the presence of renal insufficiency the inorganic phosphorus in the serum usually shows a marked increase. Serum phosphatase is high in primary hyperparathyroidism, especially in the ultimate stage (usually 8 to 40 Bodansky units). It is worthy of note that this holds true only of the osseous type of primary hyperparathyroidism (see under renal type). It is in general indicative of decalcification of the skeleton and thus not only characteristic of hyperparathyroidism.

In primary hyperparathyroidism the calcium and phosphorus balance is negative, which means that considerably greater quantities of calcium and phosphorus are eliminated in the urine than would correspond to the calcium and phosphorus intake. As soon as renal insufficiency sets in, the calcium elimination in the urine becomes reduced while greater quantities are eliminated in the feces (Albright, Aub, and Bauer). A negative calcium and phosphorus balance alone is not, however, characteristic of primary hyperparathyroidism.*

On perusal of the literature it appears that even today, after it has been established by the Boston group that the renal type is steadily increasing, in the international literature the classical type of hyperparathyroidism is the most common.

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*Regarding the various biochemical aspects referred to, it should be pointed out that Jaffe and Bodansky (1943) described as normal calcium values in the serum, fasting values for adults, 9.5 to 10.5; for children, 10.0 to 11.5; for infants, 10.5 to 12.0.

According to Woodard 10 to 11 per cent for adults is normal although values up to 12 mg. per cent have been found in normal individuals.

Jaffe and Bodansky considered a value of at least 11.5 for adults and 12.5 for children as normal. These values are to be understood as the number of milligrams per 100 c.c. of serum.

Normal values for inorganic phosphates are 2.5 to 4.0 mg. per 100 c.c. for adults, 4.5 to 5.5 for children, and 5.5 to 6.5 for infants. A drop to lower than 0.5 below normal level should be considered as indicative of hypophosphatemia while 1.0 beyond the upper limit indicates hyperphosphatemia.

Thus, for example in a review of 135 cases (1936) Wilder and Howell found all of them to belong to the classical osseous type.

Primary Hyperparathyroidism, Renal Type Caused by Adenoma. It has already been pointed out that renal complications are likely to appear when hyperparathyroidism persists for some time. However, renal primary hyperparathyroidism is the term applied to that variety which manifests itself first of all by renal symptoms even prior to skeletal changes. This form which is of utmost importance has so far been reported only by a few authors. Cope assumed that the first reaction provoked by parathormone does not occur in the bones, which could be verified in the majority of cases at the Massachusetts General Hospital. According to this author the most common type of hyperparathyroidism is the renal one (calculi) and is explained by the precipitation of calcium in the urinary tract. In 1944 Cope reviewed seventy-eight cases of his own (see Table II).

From Table II it appears that the purely renal type without osseous involvement considerably outnumbers all the others. Even before, this type had not been unknown; it is only its extent that is surprising.

TABLE II

	NO. OF CASES	PER CENT
Bone Disease		
Classic	23	30
Decalcification	1	1
Decalcification plus renal stones	11	14
No Bone Disease		
Renal stones	43	55
Total	78	100

Castleman and Mallory (1935) reviewing 25 of their own cases and 160 they collected from the literature (autopsy records) gave the statistics listed in Table III.

After this continuous series of publications referring to the subject by Cope, and also by Churchill and Cope, isolated cases of renal primary hyperparathyroidism were reported by a number of other authors too, although usually no clear distinction was made between the renal variety of osseous primary hyperparathyroidism and that renal type so frequently reported by the Boston group as occurring without skeletal changes. Such cases have been described by Schrumpf and Harbitz (1938), Higgins (1939) Fowweather and Pyrah (1938), Foulds (1944), Keating and Cook (1944), and Roth (1945). Excerpts from the case reports follow.

The case reported by Foulds, that of a woman who had had renal calculi in 1928, 1932, and 1936 but in whom the suspicion of hyperparathyroidism did not arise before 1943 when an increased calcium level of the serum was determined, also included skeletal changes (osteitis fibrosa cystica). A chief-cell adenoma of the parathyroid could be removed.

The patient described by Keating and Cook in 1944 had had renal calculi twenty-five years before with yearly recurring attacks. Twelve years before, a stone had been expelled. He suffered from polyuria and polydipsia although the Sulkowitch test was at that time negative.*

Radiographically, shadows were present in both kidneys in addition to enlargement of the kidney pelvis and calculi of the prostate. Only later did the Sulkowitch test become positive. Pemberton, who later performed an operation, found an adenoma of the parathyroid attached to the left upper lobe of the thyroid, the size of the adenoma being 2.5 by 2.0 by 0.5 cm. Prior to operation

TABLE III

	AUTHORS' OWN CASES		LITERATURE	
	NUMBER	PER CENT	NUMBER	PER CENT
Osteitis fibrosa alone	5	20	70	58.8
Renal stones alone	11	54	3	2.5
Osteitis fibrosa plus renal stones	9	36	46	38.6

*By the Sulkowitch test hypercalciuria can be determined. The test is very simply performed: 2.5 Gm. of oxalic acid, 2.5 Gm. of ammonium oxalate, and 5.0 Gm. of glacial acetic acid are dissolved in 150 c.c. of distilled water and mixed with acidified urine. The mixture develops an opacity parallel in intensity to the degree of hypercalciuria.

the calcium level in the serum was no higher than 11.9 mg. per cent, phosphorus 2.9 mg. per cent, and phosphatase 8.1 Bodansky units, while after operation calcium was 8.4 mg. per cent, phosphorus 4.2 mg. per cent, and phosphatase 4.7 Bodansky units. Thus, for example, in a review of 135 cases (1936) Wilder and Howell found all of them to belong to the classical osseous type.

Primary Hyperparathyroidism, Renal Type Caused by Adenoma. It has already been pointed out that renal complications are likely to appear when hyperparathyroidism persists for some time. However, renal primary hyperparathyroidism is the term applied to that variety which manifests itself first of all by renal symptoms even prior to skeletal changes. This form which is of utmost importance has so far been reported only by a few authors. Cope assumed that the first reaction provoked by parathormone does not occur in the bones, which could be verified in the majority of cases at the Massachusetts General Hospital. According to this author the most common type of hyperparathyroidism is the renal one (calculi) and is explained by the precipitation of calcium in the urinary tract. In 1944 Cope reviewed seventy-eight cases of his own (See Table II).

The most striking feature of this case appears to be the fact that although the disorder had been present for twenty-five years no typical skeletal involvement was noted. The negative Sulkowitch test was the result of a low calcium diet and it is said to be positive only in connection with a normal calcium intake.

In December, 1945, Keating and Cook of the Mayo Clinic made a very important publication reviewing twenty-four additional cases of hyperparathyroidism. After the authors had adopted the examination and observation methods of the Boston group, they were able to find, during the course of two and one-half years, the previously mentioned twenty-four cases while in the preceding fourteen years a total of only fourteen cases of hyperparathyroidism had been detected at the Mayo Clinic.

These twenty-four cases were grouped by the authors as follows.

1. Seven cases, 29 per cent, belonging to the classical skeletal type of hyperparathyroidism. Three of them involved renal calculi and two others calcification of the renal parenchyma.

2. Nine cases, 38 per cent, showing minimal or atypical demineralization of the skeleton. All these patients had or had had renal calculi.

3. Eight cases, 33 per cent, having renal calculi without recognizable skeletal involvement.

Summing up, therefore, bone changes were present in 67 per cent of the cases while in 92 per cent there were either renal calculi or calcification of the kidneys. Fourteen out of the twenty-four patients had previously undergone a total of twenty operations for renal calculi so that it seems justified to search for hyperparathyroidism if a patient reports recurring attacks of calculi (Cope).

The authors concluded by verifying Albright's earlier statement: (1) Hyperparathyroidism is more common than generally supposed; (2) renal involvement is more frequent and diagnostically more important than osseous involvement; (3) every patient who has renal calculi should be suspected of having hyperparathyroidism.

Studying separately the purely renal cases without osseous changes reported by Keating and Cook and Churchill and Cope, as well as by Cope alone, and comparing them with those of the classic type, it is first of all noticed that the biochemical changes are much more pronounced in the classic skeletal variety. This applies in the same measure to the increase of the calcium level of the serum as to the lowering of the phosphorus and the increase of the phosphatase values. Keating and Cook, for example, reported calcium values of less than 12.5 mg. per cent in twelve out of twenty-four cases. Of a greater diagnostic value, although not so distinctive, are the low phosphorus proportions. In the purely renal cases the alkaline phosphatase was normal.

Considering that in the second group, too, the radiograms showed only decalcification or fibrosis of the skeleton as determined by Camp and Ochsner and that in the third group the bones were altogether normal, we should ask ourselves with what degree of certainty the diagnosis of hyperparathyroidism can be established. Thus, operations were for the greatest part performed only on the strength of repeatedly determined slightly changed biochemical values and it should not surprise us that at the same time when the twenty-four patients with hyperparathyroidism were operated upon with positive result, six others underwent operation in which the suspicion of hyperparathyroidism could not be verified. The question is whether it would not be advisable to include still other diagnostic methods as, for example, the chronaxia test or the Hamilton test (Schwartz, see Baine and Rivoire).

In those cases in which operation gave a positive result it was always an adenoma (in one of the cases two) that was found. None of the patients had hyperplasia of all parathyroids, which adds to the value of these findings. In three of the patients the tumor could be palpated prior to operation. In all of them its localization was at the neck and never in the mediastinum.

The divergency between these findings and those reported by Cope (20 per cent of cases with tumors in the mediastinum) is noteworthy.

Microscopically, the renal type of hyperparathyroidism is not distinguished from the classical one by preponderance of any kind of cells in the histologic structure of the adenoma.

Following operation the calcuim level always dropped considerably and the phosphorus values returned to normal.

The establishment of a renal type of primary hyperparathyroidism has thus become an important clinical-pathologic fact. Its diagnosis is possible only by careful observation and repeated biochemical examinations. The Sulkowitch test considerably facilitates the diagnosis. By discovering hyperparathyroidism in cases of this kind, although we cannot spare the patient a renal operation, we are probably able in a number of cases to forestall recurrences.

It seems, therefore, opportune to discuss the relationship between *nephrolithiases and hyperparathyroidism.* It has been pointed out that in the classical type of osseous hyperparathyroidism of long standing, lithiasis supervenes and may by way of uremia be responsible for a fatal outcome. I saw this happen in my first case in 1926 and also in 1932. Here lithiasis must be considered the final stage. It has, however, also been observed that calculi were the first sign

of hyperparathyroidism even preceding osseous changes. Snapper (1943) commented as follows on the purely renal initial type of hyperparathyroidism:

> The human skeleton contains approximately 900 Gm. calcium. Even in the presence of a markedly negative calcium balance the daily loss of calcium does not exceed about 0.5 or maximally 1.0 Gm. Thus several months or even years may elapse before changes become apparent in the bones. But this is also the reason why skeletal changes may be preceded by lithiasis owing to the excretion of calcium and phosphorus in the urine.

We are thus confronted with the question as to whether by abolishing the state of hyperparathyroidism, that is, by removing a parathyroid adenoma, we are in a position to forestall the further formation of renal calculi and to reduce the number of relapses after operation for calculi.

Naturally, recurrences after operations for calculi have been reduced with advancing technique. In 1915 Cabot and Crabtree reported 56 per cent of recurrences after nephrotomy and 51 per cent after pyelotomy. In 1922 Barney reported 32 per cent for the same hospital. By 1924 the number of recurrences at the Mayo Clinic (Braasch and Foulds) had been lowered to 10.79 per cent. Other authors listed 14.9 per cent, after pyelotomy, 32 per cent after pyelonephrotomy, and 29.4 per cent after nephrotomy (1937). A synopsis of results was given by Clement in 1940. As a matter of course, only part of these cases can be attributed to hyperparathyroidism since infection, stasis, operative trauma, and other unknown sustained traumas certainly play an important role although we do not know to what extent.

However, in 1934, attention began to concentrate on the relationship between renal calculi and hyperparathyroidism. Barney and Mintz pointed out that in 4 to 5 per cent of cases hyperparathyroidism plays an important etiologic role in lithiasis. Griffin, Osterberg, and Braasch attribute only 0.2 per cent of their cases of renal calculi to hyperparathyroidism, based on biochemical examinations of 1,026 patients. Cope reported 10 to 15 per cent. According to Keating and Cook cases of renal calculi caused by hyperparathyroidism constitute but 2 per cent of the total for the period during which they studied renal hyperparathyroidism. Snapper pointed out that in Amsterdam oxalate stones are much more frequent than calcium phosphate stones. None of his patients with recurrent stone attacks, however, presented hypercalcemia or hypercalciuria.

My experience at a hospital in Palestine where, as everywhere in the Near East, renal lithiasis is extraordinarily common was a similar one. For a long time we have tried in vain, lately by means of the Sulkowitch test, to establish hypercalciuria in recurrent renal calculi, recurrences occurring here in Palestine after operation in 20 per cent of cases. None of the cases so far yielded the least indication, in history, clinically as well as biochemically, of hyperparathyroidism. In some cases the Sulkowitch test was slightly positive, but subsequent biochemical examinations (Ca, P) revealed nothing pathologic.

In only one autopsy made on a patient who had suffered from calculi and had been operated upon in my department was a parathyroid adenoma detected.

CASE REPORT

The history was that of a man 45 years of age at the time of his death. He came to Palestine five years before and soon afterward he experienced urinary trouble for the first time. The symptoms were typical of stones in the kidney and bladder. About two years before he had been operated upon, stones being removed from the left kidney by nephrotomy and from the urinary bladder by a sectio alta. After the operation the patient felt well up to two months before death.

He then had an attack of renal colic on the right side, which was the side not operated upon. A roentgenogram was taken which revealed the presence of large stones in the right, smaller ones in the left kidney.

A right nephrotomy was performed and a large stone removed which had broken up into three fragments. The chemical laboratory reported that the stones were composed chiefly of ammonium-magnesium-phosphate.

The patient seemed to recover satisfactorily until an apparently latent intestinal infection (bacillary dysentery) manifested itself on the fifth day after operation. From that time on rise in temperature, diarrhea, and collapse caused a steady downward course for the next seven days until the death of the patient.

An autopsy was performed. Necrosing colitis and bronchopneumonia with abscess formation were established as the cause of death.

The most interesting findings were those in the cervical region. The thyroid gland appeared normal except for a small adenoma in the right lobe and moderate enlargement of the pyramidal lobe. Near the right lower pole of the gland an oval nodule was discovered connected with the thyroid gland by a stalk which was composed of blood vessels and fat tissue.

On *histologic* examination the described node proved to be composed of parathyroid tissue. There were no fat or oxyphile cells present as might be expected in view of the patient's age. The node was composed mainly of chief cells and of the so-called water-clear cells.

It was decided that this was a true adenoma of parathyroid tissue, and, therefore, most likely primary hyperparathyroidism, apart from histologic considerations, mainly for two reasons:

1. The size of the parathyroid nodule was much larger than ever seen in cases of secondary hyperplasia of the parathyroids encountered in different conditions of the skeleton as well as in chronic nephritic lesions.
2. There was no enlargement of the rest of the parathyroid tissue which should be expected in case of secondary involvement of the glands.*

The x-ray picture of the lumbar spine, the pelvis, and the hip region was negative.

In Vienna, where I used to work, I explored the neck region operatively and searched for a parathyroid adenoma in two cases of recurrent renal calculi (Mandl, 1938). Biochemically there was no indication of hyperparathyroidism and the bones were also normal. I am unable to give exact details of the one case. I have been in communication with the second patient, who now lives in New York.

The history of this patient, who had been in a German concentration camp where he had been kicked in both sides and sustained a renal hemorrhage, told of renal calculi in both kidneys later in 1936. The stones consisted of calcium and phosphate. On operation neither a parathyroid adenoma nor hypertrophy of the parathyroids was found. Therefore, after it was concluded that there were actually four normal parathyroid glands, two of them were removed. Four years after this operation the patient wrote from New York that he had become worse, had frequent colics, and was thus incapable of attending to his business and was confined to bed.

*I am obliged to Dr. Ungar of the Institute of Pathology and Histology for kindly placing this autopsy record at my disposal.

Radiograms taken at this time, compared with earlier ones, showed marked increase of stone formation in both kidneys. The stones were now and then expelled with or occasionally even without colic. According to latest results of examinations the renal function was nevertheless satisfactory. An acid diet was prescribed for the patient and he was advised strictly to avoid calcium and phosphates. The kidney pelvis was irrigated with trypaflavine. Acidification of the urine proved difficult. He had often been advised to submit to operation but this operation had never been performed.

In Vienna the findings had been as follows: Serum calcium 10.8 mg. per cent; phosphorus 2.95 mg. per cent; calcium in the urine 105.6 mg. per cent; phosphorus in the urine 20.8 mg. From New York the following data were received: creatinine 1.04; nonprotein nitrogen 30.6; calcium 11.2; phosphorus 2.84; total protein 6.04; phosphates 2.4. Since 1942 nothing further has been heard.

The relationship between renal calculi and hyperparathyroidism is of extraordinary importance and in the future the detection of primary hyperparathyroidism in a greater number of cases may possibly help to an appreciable extent to avoid the recurrence of calculi. However, it would be of even greater importance to forestall a further osseous development by an early diagnosis and early institution of treatment of hyperparathyroidism.

It must be mentioned, that, apart from calculi caused by hypercalcemia and hypercalciuria, these pathologic changes may also be responsible for the precipitation of calcium in the renal parenchyma (nephrocalcinosis). Cases of this kind have been described and collected from the literature by Albright, Braid, Cope, and Bloomberg. Those published after 1934 have been reviewed by Snapper (1943).

The Gastrointestinal Type of Primary Hyperparathyroidism Caused by Adenoma or Hyperplasia of the Parathyroids.—It is not yet certain whether there exists a gastrointestinal type of hyperparathyroidism similar, for example, to the renal type in which the other classical manifestations are pushed to the background and gastrointestinal symptoms dominate the scene. Lièvre (1932) was the first to describe a variety of hyperparathyroidism with severe gastrointestinal manifestations which he witnessed in two of his patients who, however, otherwise had the classical osseous type. In both, a parathyroid adenoma was removed with good result.

In Lièvre's second case there were major crises at intervals of about a fortnight during which the patient, under constant vomiting, was intolerant to any kind of food.

Lièvre's third patient also developed *crises gastriques* recurring every two, three, or four weeks characterized by vomiting and painful abdominal colic. This patient, however, also had classical osseous hyperparathyroidism with parathyroid adenoma.

Similar cases have been described by Hunter, Pemberton, and Geddie, Barr, Bulger, and Dixon. One reported by Ask-Upmark included considerable congestion and retention of the gastric contents when a roentgen examination was made because of gastric symptoms accompanying hyperparathyroidism. However, all cases outlined here were of the classic type associated with gastrointestinal manifestations.

A different condition is that referred to by Morelle. His patient had been admitted to the hospital with intestinal obstruction and all signs of ileus.

The calcium level of the serum was 19.7 mg. per cent. After this had been established, an examination was made of the skeleton where, however, only moderate decalcification was found. Since vomiting increased in intensity, the neck region was explored operatively and a parathyroid adenoma detected. After operation the patient rapidly recovered and all symptoms disappeared.

Snapper (1943) quoted from the Dutch literature a similar case reported upon by Beyerink. Here, too, the condition was clinically characterized by attacks of vomiting. Calcium in the serum was 19.3 to 21.0 mg. per cent; phosphorus 2.0 to 2.5 mg. per cent. X-ray findings were normal.

The skeleton and kidneys being normal, the two cases must be considered as typical gastrointestinal types of hyperparathyroidism.

Renewed attention has recently been drawn to this form of hyperparathyroidism by Rogers, who described two patients having a rather acute course. In both, autopsy revealed duodenal ulcer. These two cases are interesting because of the overlapping of the two diagnoses, ulcer and hyperparathyroidism (Gutman and Parsons), and further because of the fact that in hyperparathyroidism a diet rich in calcium and phosphorus as it is prescribed for ulcer may aggravate the general symptoms of hyperparathyroidism. The danger of this diet in the presence of hyperparathyroidism has also been emphasized by Hunter and Aub, Albright, Bauer, Claflin, and Cockrill.

In one of Rogers' two cases, both aggravated by ulcer diet, an adenoma and in the other primary hyperplasia of the parathyroid glands was found.

Primary Hyperplasia of all Parathyroid Glands With Osseous, Renal or Gastrointestinal Involvement.—The whole concept of hyperparathyroidism, implying a rejection of the idea of a compensatory parathyroid hyperfunction in certain osseous diseases, has become confused by the fact that there may also be a primary diffuse hyperplasia of all parathyroid glands creating a clinical picture exactly similar to that caused by isolated adenomas. The same applies to the presence of two or several adenomas. Even before 1934, when Albright, Bloomberg, Castleman, and Churchill were the first to refer to three cases of this type particularly, autopsy records had been made available in which osteitis fibrosa generalisata was associated with multiple adenomas or enlargement of all parathyroid glands (Schmorl, Molineus, Hoffheinz, Goedel, Paul, Bergstrand, and Hanke.

There was also reference to two operations: Hellström, in 1931 after having removed one parathyroid adenoma without success, on the occasion of a second operation found another one, the removal of which effected definite cure. In a case published by Hunter in 1931, operation revealed two normal parathyroid glands but also two adenomas which could be removed while the normal organs were left untouched. A similar case was described by Abel. The clinical aspect of all these cases was that of the classic osseous hyperparathyroidism (see Albright and associates, 1934).

However, the cases published by Albright and co-workers in 1934 with hyperplasia of *all* parathyroid glands presented quite a new picture, markedly different from that known up to then. The outstanding feature of these cases,

as it appeared, was the association of hyperplasia of the entire parathyroid tissue with the renal form of hyperparathyroidism in the absence of any sign of osseous involvement. This alone at first let it appear justified to speak of a separate variety of the disease. As a causative factor at that time an underlying pituitary disorder was suggested stimulating the function of the entire parathyroid system so that more hormone was produced than required by the organism. It was pointed out that histologically the cases were characterized by an increase of the water-clear cells in contrast to the increase in the number of chief cells as it occurs in ordinary adenomas. This hyperplasia of the entire parathyroid system was later corroborated by others although with certain restrictions. At the Massachusetts General Hospital, in 1944, Cope found among his seventy-eight patients with hyperparathyroidism seven with hyperplasia of all four parathyroid glands, an occurrence that has been compared to a general hyperplasia of the thyroid tissue in hyperthyroidism.

On the other hand, in 1944 Cope pointed out that the clinical picture of diffuse parathyroid hyperplasia was in no way different from that of isolated parathyroid adenomas since all characteristics arising from the presence of an adenoma were also encountered in diffuse hyperplasia (osseous and renal type).

Regarding the cause of this hyperplasia, Cope was unable to furnish further information beyond the fact that the search for disturbances in the pituitary function had been in vain.

The histologic picture described by Cope, however, was the same as that referred to by Albright and co-workers in 1934: hyperplasia and hypertrophy of the water-clear cells which occasionally had assumed sixty times their original size.

Cope pointed out that at operation these changes are easily recognizable but he recommended, nevertheless, making frozen sections during the operation in order to establish the diagnosis beyond any doubt.

It might be assumed that owing to the preponderance of the renal type of the disease diffuse hyperplasia should be very common. This could not, however, be verified by the studies performed at the Mayo Clinic. Here the twenty-four cases reported upon by Keating and Cook (1945) included twenty-three cases of isolated and one of multiple adenoma while none of them involved primary hypertrophy of the entire parathyroid tissue. It should be recalled that the cases referred to by these authors were predominantly of the primary renal type or at least of secondary lithiasis. It was not before 1946 that Rogers gave an account of the first case of primary hyperplasia of the parathyroid glands observed at the Mayo Clinic. This was one of the cases with gastrointestinal manifestations and association with duodenal ulcer. Here, too, the water-clear cells were encountered.

Summing up, it may, therefore, be said that diffuse primary hyperplasia of the parathyroid tissue is much less common than isolated adenomas (Lage and Greene, 1943). Its clinical manifestations are the same as those provoked by isolated adenoma (osseous, renal, and gastrointestinal form). The cause

of this diffuse hyperplasia, although of greatest etiologic interest, is as yet imperfectly understood. The cell type characteristic of diffuse primary hyperplasia of the parathyroid tissue is that of the water-clear cells described by Getzova.

PRIMARY AND SECONDARY HYPERPARATHYROIDISM

A short historical review may precede the discussion of this important question. In 1907, when Erdheim published the important results of his studies on parathyroid "hyperplasia," at first no difference was made by pathologists between enlargement, hyperplasia, adenoma, or tumor of the glands. The condition was generally referred to as hyperplasia and Erdheim himself (1907) mentioned it in his report of three cases of osteomalacia. But there was also reference to a "tumor" 3.6 by 2.0 cm. in diameter. Whether a clear distinction was at that time made between osteomalacia and osteitis fibrosa generalisata is not clear. Hyperplasia of this kind was, however, noted by Erdheim and others in osteomalacia as well as in rickets, in men and in rats where it had been produced experimentally. These observations which were then even extended to Recklinghausen's disease formed the basis of Erdheim's theory, implying that hyperplasia was here the result of the decalcification of bones and, therefore, of a compensatory nature. Larger quantities of hormone would be produced, warranting the normal ossification of the bones, and decalcification was halted.

When after the first successful parathyroidectomy a decisive therapeutic effect was noted I defined my opinion regarding the theory of this operation as follows (Mandl, 1926):

> Important objections have been made against Erdheim's theory which followed as a logical conclusion from his basic experimental studies. First of all, it seemed odd that the supposed hyperplasia, considered a compensatory hypertrophy by Erdheim, should in the vast majority of cases be found only in one instead of several or all parathyroid glands. Hoffheinz found no more than four cases, i.e., 15 per cent, in the literature in which enlargement was reported for more than one of the glands; and 85 per cent, therefore, presented involvement of no more than one of them. Erdheim defended his opinion by pointing out that enlargement of one single gland was sufficient to meet the exaggerated functional requirements. This explanation should, in my opinion, be rejected since actually the enlargement of one single gland is by no means able to control the calcium metabolism in a way that no pathological manifestations would arise. On the contrary, we know from observation and from post-mortem studies on individuals who died from osteitis fibrosa generalisata that in spite of enlargement of one parathyroid gland their calcium metabolism had been completely deranged. It is equally impossible to presume that nature which usually provides so generously for the compensation of an abolished function should not make use, in an emergency, of the vast reservoir of the three remaining normal parathyroid glands. It might further be pointed out that in several cases the parathyroid enlargement definitely presented the character of a new growth. Genuine new growth, however, can by no means be considered a compensatory action for an abolished function."

The successful extirpation of the parathyroid adenoma seems to have verified my opinion.

On the other hand, Snapper was right when he pointed out that in view of the results of the first parathyroidectomy for Recklinghausen's disease the entire problem seemed simplified. Today it is generally known that in fact this only seemed so, and a general rejection of the idea of a compensatory secondary hyperparathyroidism is no longer justified.

It is a generally established fact, verified by experience from all over the globe, that Recklinghausen's and other diseases are no doubt caused by primary hyperparathyroidism, which means that in the vast majority of cases one or two parathyroid adenomas or diffuse hyperplasia of the entire parathyroid tissue is the responsible causative factor. However, what cases develop adenomas and when hyperplasia of the parathyroid tissue occurs are not yet understood although there is no longer any question regarding their causative nature.

On the other hand, Erdheim's theory has regained its validity for that type of case which on the strength of experimental and clinical studies must be considered a secondary hyperparathyroidism.

This experimental secondary hyperfunction of the parathyroids can be provoked in various ways, by D avitaminosis as well as by withholding ultraviolet rays from chickens, decalcification of bones and parathyroid hyperplasia were obtained (Doyle, Nonidez and Goodald, Higgins and Sheard, Sheard, Higgins and Wilder). The parathyroids grew to ten times their normal weight. Addition of cod liver oil, irradiation with ultraviolet rays, or administration of parathormone prevented this hyperplasia.

According to Oberling and Guerin, by raising chickens in the dark or by withdrawing calcium from their diet, parathyroid hyperplasia can be produced and is due to proliferation of the water-clear cells.

By means of a biliary fistula and a consequently disturbed absorption of fat, Duttmann, Tamman, Dieterich, and Loewy were able to effect decalcification and secondary hyperplasia of the parathyroids (see Snapper, 1943).

From a clinical viewpoint it should be emphasized that even today the parathyroid hypertrophy existing in osteomalacia is, in accordance with Erdheim's findings, regarded as a secondary manifestation.

Further, multiple myeloma may occasionally effect secondary parathyroid hypertrophy. These myelomas cause decalcification of bones so that hypercalcemia and hypercalciuria may develop and the picture of Recklinghausen's disease thus may be simulated. Cases of this kind have been referred to repeatedly in the literature. However, none of Snapper's nine patients showed increased calcium values in the blood. It is not particularly surprising that in the presence of myelomatosis, as soon as renal insufficiency supervenes, the phosphorus in the serum rises. Conditions are here similar to those prevailing in primary hyperparathyroidism. Regarding differential diagnosis, Snapper pointed out that in myelomatosis the serum phophatase values are not increased. It must be admitted, however, that secondary parathyroid hyperplasia developing as a result of these biochemical changes is rare and that it is by no means a characteristic of this disease. However, this kind of secondary hyperplasia

has, for example, been referred to by Barr, Bulger, and Dixon. Similar findings have been reported by Piney and Riach.

In extensive carcinomatous bone metastases, as a consequence of maligant disease of the bone, the destruction of the skeleton is similar to that of the previously mentioned disorder. Occasionally hypercalcemia and hypercalciuria may also develop. I have seen two cases of this kind in which, however, autopsy revealed no hyperplasia of parathyroid tissue. Important data regarding that point have, however, been published by others. Thus, for example, Mason and Warren gave an account of a patient on whom an operation had been performed for mammary carcinoma five years earlier. The radiogram showed carcinosis of the entire skeleton. Nevertheless, the neck region was explored operatively and metastases were detected in the thyroid and parathyroid. In these authors' opinion the marked degree of hypercalcemia in this case either was connected with an associated hyperparathyroidism or, on the other hand, was due to the extensive destruction of bones. I am inclined to share the latter assumption as being the more probable one.

An exceptional case is that reported by Klemperer since this author was the only one to detect a parathyroid adenoma instead of diffuse hyperplasia of all parathyroids secondary to bone metastases after mammary carcinoma. Destruction of the bone tissue was complete and had in Klemperer's opinion been responsible for the formation of one isolated parathyroid adenoma. As I pointed out in 1926, compensatory hypertrophy is conceivable only if it involves the entire parathyroid tissue and it appears that here, in accordance with Snapper's view, we are dealing with a "mild degree of Recklinghausen's disease with a parathyroid tumor" in addition to extensive bone metastases after mammary carcinoma.

The following case described by Ben-Asher (1939), therefore, represents a logical development:

A man 58 years of age was admitted to the hospital with vague complaints. Radiography revealed a large multilocular cyst of the right humerus, while the skull showed multiple areas of rarefaction. A similar picture was found in the bones of the pelvis, the right femur, and both fibulas. Although everything pointed in a direction of bone metastases, hyperparathyroidism could not be excluded. Continuous examinations after a test diet revealed persistent hypercalcemia and low phosphorus levels in the blood in addition to hypercalciuria. Therefore, an operation was performed and at the right side of the neck two markedly enlarged parathyroids were found and removed. Although the patient survived the operation the calcium level of the blood remained unchanged. Since the condition was not improved, a second operation was done in order to detect similar changes on the left side of the neck, but without result. Ten months later the patient died; no autopsy was made.

The case was one of secondary hypertrophy of the parathyroid, the removal of which, therefore, was unlikely to effect improvement.

The cases outlined in the foregoing are more interesting in a differential-diagnostic respect than regarding the secondary hyperparathyroidism which may occasionally appear in such cases.

More important and frequent are those cases which today dominate the field of secondary hyperparathyroidism, in which either in children or in

adolescents renal osteodystrophy occurs and results in enlargements of all parathyroid glands. Usually on the basis of a congenital defect, some type of urinary insufficiency develops (congenital defect of renal development, polycystic kidney). In view of the fact that the osseous changes eventually lead to deformity, stunted growth, and infantilism, this condition has been referred to as renal rickets.

Far less common is secondary renal hyperplasia of the parathyroids in adults. Occasionally an exceptionally chronic course of glomerulonephritis, congenital polycystic kidney, or even bilateral renal calculi may be accompanied by extensive fibrosis or porosis of the skeleton with secondary hyperparathyroidism. Juvenile cases of this type have been described by Parsons, Mitchell, Park and Elliot, Derov and Brodny, and others (see Snapper, 1943).

Hubbard and Wentworth (1920) were the first to describe renal dystrophy in adults. Detailed reports followed by Albright, Drake and Sulkowitch. Parathyroid hyperplasia subsequent to renal failure was reported by Bergstrand in 1931. This author found parathyroid enlargement in ten out of fifty cases of chronic glomerulonephritis.

According to Snapper, preconditions for parathyroid enlargement in cases of this kind are (1) that renal failure must be of long duration, and (2) that the renal failure must give rise to acidosis.

In Snapper's book we find a synopsis of thirteen cases, the patients ranging in age from 2 to 45 years. Very important are the biochemical data: In none of the cases was the calcium level of the blood increased while inorganic phosphorus in the serum was always high. Parathyroid hyperplasia was in all cases characterized by proliferation of the chief cells and the water-clear cells (Lindsay). The underlying disease was in the urogenital tract. The majority of the patients had fibrosis of bones, and calcification of blood vessels was very common.

In 1942, Sussman and Poppel gave a report on six cases of secondary parathyroid hyperplasia. The ages of the patients were 6, 12, 14, 18, 21, and 42 years, respectively. They all had renal insufficiency and a great part of them also had skeletal decalcification. The calcium values in the serum were normal or only slightly increased, while phosphorus was invariably high. Where postmortems could be made the parathyroids were always found enlarged.

In the presence of secondary hyperparathyroidism, parathyroidectomy is futile.

In this hospital a case of this type was observed in 1946 (Medical Department A) by Ullmann and Schorr.

A girl aged 12 years had a hypoplastic kidney of the type similarly found in several members of her family. She died from uremia, and on autopsy hypertrophy of all parathyroid glands was found as well as bone changes typical of osteitis fibrosa (microscopically).

The laboratory findings, a short time before she died, were urea 500 mg. per cent; uric acid 8.3 mg. per cent; alkali reserve 14.7 vol. per cent; calcium 9.7 to 10.4, phosphorus 5.0 to 6.0 rising to 10.2 to 13.8 mg. per cent; phosphatase 10.2 to 10.3 Bodansky units; creatinine (qualitative) +++, xanthoprotein 100.

Radiographically the bones were normal; there was neither decalcification nor deformities. The "dwarfism" consisted in retarded growth (122 cm. instead of 150 cm.) and deficient weight (22.5 kg. instead of 40 kg.).

The synopsis given in Table IV seems important from a practical viewpoint, illustrating the main differences between primary and secondary hyperparathyroidism.

In a diagnositic respect conditions are not so simple as it would appear from Table IV, owing to the fact that in primary and also in secondary hyperparathyroidism, in the former especially as a result of latest studies, the renal character of the disease so frequently holds the foreground. If a patient is suffering from hyperparathyroidism caused by parathyroid adenoma, he may develop renal insufficiency at a comparatively early stage which in turn may stimulate an even more pronounced hyperfunction in the parathyroids. In this way the degree of hyperparathyroidism may not only become intensified but the difference between primary and secondary parathyroid hyperfunction may become blurred. On the other hand, as pointed out by Jaffe, in a case starting as one of secondary hyperparathyroidism subsequent to renal disease, the parathyroid hyperfunction may become so excessive that it exerts a marked influence on bones as well as on the already existing renal insufficiency. Here biochemical studies are of no great avail as it is seen, for example, in a case reported by Cope in 1944:

A man, aged 68 years, entered the hospital April 27, 1940, to receive roentgen-ray therapy to a basal-cell carcinoma of the scalp. He had additional complaints; for the previous

TABLE IV

PRIMARY HYPERPARATHYROIDISM	SECONDARY HYPERPARATHYROIDISM
Clinical Type	
Osseous	Osseous (osteomalacia, myeloma, carcinoma)
Renal	Renal (congenital lesion, hypoplasia, chronic glomerulonephritis, renal failure with acidosis); renal form in children and adolescents, rare in adults
Gastrointestinal; only adults	
Biochemical Findings	
Marked hypercalcemia	Hypocalcemia
Inorganic phosphorus in serum low	Inorganic phosphorus high
Phosphatase high	Phosphatase high
Bones	
Spontaneous fractures frequent	Fractures very rare but deformation of bones frequent
Radiography	
Cysts and tumors	Porosis or fibrosis
Parathyroid Findings	
Usually one, rarely two adenomas; hyperplasia rare	Only hyperplasia
Histology	
Adenoma: various cell types usually chief-cell adenoma	Chief-cell and water-clear cell hyperplasia
Primary hyperplasia: mostly water-clear cells	
Operation	
Early operation indicated	Operation contraindicated

one and one-half years weakness, especially of the legs, had been progressive, and for the previous few months the patient had been bedridden. Neurological study showed no reason for the weakness.

Lateral roentgenogram of the skull showed diffuse small rarified areas. Spine and pelvis were diffusely decalcified with a single cystlike area in the second lumbar vertebra and another in the crest of the ileum. Diagnosis was multiple myeloma.

Chemical findings revealed no Bence-Jones protein and no elevated serum protein as would be expected in multiple myeloma. Blood serum calcium level was 11.2 per cent, serum phosphorus 5.3 per cent, and phosphatase 17.1 Bodansky units. There was a moderate amount of calcium in the urine and intermittent albumin. Serum protein was 6.4 Gm., nonprotein nitrogen 29 mg., and uric acid 6.6 mg.

A tentative diagnosis of primary hyperparathyroidism with secondary impairment of the renal function was made. Upon repeated examinations, calcium and phosphorus values were practically unchanged. The phosphatase rose further to 19 to 22.5 units. Later roentgenograms showed decalcification of the bones of the extremities. The medical service decided that the patient probably had primary renal disease with secondary hyperparathyroidism. The surgical service on the other hand, judged the hyperparathyroidism to be primary, basing the decision on the slightly elevated serum calcium level (11.3 mg. at the highest). Had the parathyroid overactivity been initiated by the phosphate retention, the calcium level should still have been below normal. Operation was not advisable, however, since the renal disease had progressed to such an extent that some degree of hyperparathyroidism was thought necessary to maintain the calcium level.

The elevated phosphate level would depress the calcium once a tumor was removed and the other parathyroid glands would undergo secondary hyperplasia. One form of hyperparathyroidism would be exchanged for another.

After discharge, the patient entered the hospital again on May 15, 1942, with a diagnosis of pyelonephritis to which he succumbed on June 6, 1942.

At post-mortem examination, an encapsulated adenoma of the right upper parathyroid was found, measuring 22 by 6 mm. and weighing 2.4 gm. The three other glands were normal. Giant cell tumors and cysts were found. There was decalcification of the ribs. The kidney parenchyma had been severely damaged. There was calcification of the lungs.

This patient illustrated the difficulty of making a diagnosis between primary and secondary hyperparathyroidism in the presence of impaired renal function.

The post-mortem findings proved that the primary form of the disease was present since he had an adenoma of the parathyroid and three uninvolved glands.

Although there is today no longer any doubt as to the existence of a secondary type of hyperparathyroidism, it should be borne in mind that it is extraordinarily rare and should be taken into account especially if the leading feature of the clinical picture is renal disease (setting aside the destructive bone diseases referred to previously).

CASES OF HYPERPARATHYROIDISM WITH SPECIAL CLINICAL FEATURES

Mention should be made of the fact that hyperparathyroidism may run an extremely protracted course and parathyroid tumors may be present without provoking any clinical manifestations while, on the other hand, there is a very acute toxic type of hyperparathyroidism that may very soon become fatal. These are the two extremes but are both of great importance.

Silent or Inactive Tumors of Parathyroids.—Cases of this kind listed in the literature up to the year 1932 have been collected by Lièvre with addition of one

of his own cases. These cases were reported upon by Léri, Faure, Beaulieu and Ruppe, Léri and Linopier, Pareira and De Castro Freire, Hirsch, and Willich. The latter gave an account of the case of a woman 56 years of age who had had symptoms for twenty-six years, after which spontaneous cure occurred. Since then cases of this kind have again and again been reported. Thus, for example, Keynes performed an operation in a 50-year-old woman on a hard swelling of the left side of the neck, removing the growth, which showed no attachment to neighboring organs. The tumor weighed 18 Gm. and had, histologically, a normal parathyroid structure consisting exclusively of oxyphil cells. Radiograms of the skeleton made after the operation revealed nothing of importance. Keynes thought he was dealing with an inactive parathyroid tumor.

Barker and Brines described the case of an 18-year-old girl who had complained of abdominal symptoms and on whom an appendectomy was performed. The authors subsequently removed a tumor, 2.5 cm. in diameter, at the level of the cricoid cartilage. The microscopic diagnosis was hyperfunctioning parathyroid adenoma.

Roentgenograms taken later showed, in various parts of the skeleton, fine granular mottling even leading to cyst formation in four sites. Another roentgenogram taken seven months later showed that the cysts had vanished.

Spontaneous cure of osseous hyperparathyroidism was reported by Oestling. Occasionally after a period of apparent remission the process may resume its progressive character and become fatal (Linden).

In Coburn's case the patient, after sixteen years of suffering from symptoms indicative of hyperparathyroidism, developed—in the author's opinion, owing to the fact that the disease was not recognized—a tumor in which the operation, although it was done late, nevertheless was done in time. The tumor was found in the mediastinum. The case had been of the osseous and renal type.

Acute toxic and Cachectic Types of Hyperparathyroidism.—Even Lièvre in his monograph referred to a *forme cachectique de l'osteose parathyroidienne,* adding several examples. At a comparatively early time (1931) such a case was described by Bergstrand.

Two similar cases of this *forme cachetique* were described by Wanke (1930). His first patient died within six months after treatment by curettage for localized osteitis fibrosa which had been localized four years previously. On autopsy, osteitis fibrosa generalisata was found in addition to a parathyroid tumor of a benign type. In this as well as in his second case, in which no operation was performed but which under the signs of progressive cachexia led to a fatal outcome, the microscopic findings were of a parathyroid tumor consisting of chief cells.

Even in the operative era when the recognition of the disease had become more general, interesting cases of acute hyperparathyroidism were reported. The first was that of Lowenburg and Ginsburg (1932) in which acute hyperparathyroidism developed following the administration, by error, of 100 units of parathormone. On the second day the 5-year-old boy became listless and started vomiting. On the fourth day he developed severe mental depression with

high temperature and tachycardia. On the sixth day the mistake was discovered and he improved rapidly. At that time calcium in the blood serum was 19.6 mg.

Another case of acute hyperparathyroidism quoted in the literature is that by Hanes. Whether or not the diagnosis was justified here is doubtful in view of the fact that the patient had had the signs of hyperparathyroidism for five years with typical osseous changes and metastatic renal calcification. When he was prepared for operation he became progressively weaker, began to have a fever, and died before the operation had been performed. On autopsy, a parathyroid adenoma was found in addition to extensive calcification of connective tissue, especially in the kidneys and myocardium, and to a lesser extent in the lungs and stomach. With reference to this case, Albright pointed out that the acute toxic condition develops after the blood calcium has exceeded a certain limit. This is accompanied by a simultaneous rise of the phosphorus values (while they usually drop in typical hyperparathyroidism) "because phosphorus is no longer diffusible at very high levels of calcium." According to that author, therefore, the alarming symptom is not the high calcium level in the blood but rather the abnormally high phosphorus. It should be borne in mind, however, that even in the presence of extremely high calcium values the simultaneous rise of the blood phosphorus is by no means a common occurrence. Even in the presence of as high a value as 23 mg. per cent (as reported by Snapper) or even 30 mg. per cent (Cutler and Owen), phosphorus values remained low. In Snapper's opinion, it is only in the terminal stage with supervening uremia, owing to renal calculi or renal calcification, that the phosphorus values may also reach excessive proportions. It appears, therefore, that once this stage is attained the suitable moment for operation has been missed.

In 1939, Oliver gave an account of two cases of acute hyperparathyroidism with fatal outcome. The leading symptoms were of a mental and gastrointestinal nature (vomiting, constipation, and anorexia). Later the temperature became elevated, and tachycardia and high urea values supervened.

A similar case was reported upon by Smith and Cooke (1940). The patient had been suffering from a bone disease for two years. Later gastrointestinal symptoms, tachycardia, and rise of temperature suddenly supervened. The patient eventually died under the signs of uremia. Autopsy showed an adenoma composed of chief cells.

Alexander, Pemberton, Kepler, and Broders described another case of this acute type, the patient succumbing within six months.

The next case of acute hyperparathyroidism was that reported by McClure and Lam in 1945, as follows:

> Four months before the patient was admitted to the hospital, November, 1931, violent sneezing elicited a tearing sensation in the right side. Just before admission she had dyspnea, weakness, and anorexia. Examination revealed exudation at the base of the right lung, the cellular character of which was suggestive of malignancy, and a roentgenogram of the right femur also aroused the suspicion of a malignant process. After having received deep roentgen therapy, the patient was discharged on Dec. 2, 1931, but had to be readmitted on December 26, because of vomiting and anorexia. When she was again discharged a few days later, she sustained a spontaneous fracture of the left femur.

When she returned to the hospital, the calcium level of the blood was 14.3 mg. per cent and phosphorus 2.57 mg. per cent. Vomiting increased in intensity and the blood calcium rose to 19.4 mg. per cent, phosphorus to 3.88 mg. per cent. On January 20 her mental status was referred to as very cloudy. On February 13, calcium was 14.2 mg. per cent and phosphorus 6.25 mg. per cent. On February 15, the patient died.

Autopsy revealed diffuse hyperplasia of all parathyroid glands. There were further calcium deposits in the lungs, kidneys, and blood vessels. The bone picture was characteristic of an advanced stage of osteitis fibrosa cystica.

The authors were correct when they asked why hyperparathyroidism had not been suspected at an earlier stage.

Eventually, there are two further fairly acute cases reported upon by Rogers for which post-mortem findings are available and both of which involved acute intoxication.

On the whole, therefore, it appears that in a relatively large number of cases the diagnosis of hyperparathyroidism is not considered until it is too late. In my opinion, it would be advisable to perform the simple and inexpensive Sulkowitch test as a routine measure which would reveal any suggestion of hyperparathyroidism without delay. In a greater number of the cases outlined in the foregoing discussion, no calcium and phosphorus determinations had been made.

Mention has been made of the microscopic findings in the less active as well as in the more acute types of hyperparathyroidism in order to show that neither the size nor the cell character has any bearing on the clinical picture.

MALIGNANT PARATHYROID TUMORS

Those cases in which hyperparathyroidism is due to malignant tumors deserve separate mention.

In the past few years two papers have appeared dealing in a comprehensive manner with that point (Gentile, Skinner, and Ashburn, Alexander, Pemberton, Kepler, and Broders). First of all it was surprising that of the fourteen cases of Alexander and co-workers, thirteen of them, or 92.8 per cent, were referred to as malignant, while in the large series of Cope, for example, including fifty-eight cases, there was not one case of malignancy.

Apparently the classification is a purely microscopic one and the clinical picture need not always show malignant features.

In any event, the point is important enough to be dealt with in detail. Above all, for purely empirical reasons the parathyroid tumors (eight cases) described by Kocher in 1908, which were characterized by containing glycogen, should either be eliminated, from these considerations or be regarded as "not functioning malignant parathyroid tumors." Later, in 1907, Langhans published reports on four cases with tumors which he considered to originate from the parathyroids, while Harbitz thought them connected with the thyroid gland. Similar reports have been made by De Quervain, Roffo and Landivar, Fasiani, but in none of them, characteristically, is reference made to bone changes. In two cases of this type (Ferrero and Sacerdote, Alessandri) bone metastases contained parathyroid tissue and, in Alessandri's case, parathyroid along with

thyroid tissue. Other publications were made by Hendrich, Guy, Toland, Price and Mowatt, Hall and Choffin, and Armstrong. In none of the cases were indications of hyperparathyroidism found and from a purely clinical viewpoint the tumors were in no way distinguishable from those originating from the thyroid gland.

I performed an operation for a tumor of this category in 1944:

The patient was a woman 46 years of age whose father and brother had had intestinal carcinoma. The patient herself had had a goiter for many years and, especially during the past three years, had suffered from dysphagia and dyspnea. X-ray examination showed a substernal tumor on the left side displacing the trachea to the right. The basal metabolism rate was + 11 per cent. On operation, an adenoma was found attached to the left lobe of the thyroid gland, the size of an orange, extending into the substernal space and slightly attached to the esophagus. The tumor was enucleated and resected. Postoperatively there was nothing of importance.

Microscopy showed a malignant tumor containing parathyroid tissue.

In view of the result of the microscopic examination roentgenograms were made of the patient but no skeletal changes could be ascertained and the biochemical findings were likewise negative.

Follow-up examination in 1946 showed the patient in perfect health and without any complaints.

On perusal of the literature referring to these "nonfunctioning malignant tumors of the parathyroid" one finds a total of twenty-four cases reported upon until 1945. Clinical signs of malignancy, that is, the appearance of metastases, are referred to by De Quervain, Guye, Toland, Price and Mowatt, and Hall and Choffin. Follow-up examinations, where they could be performed, had usually an unfavorable result. Although, therefore, the tumors were of a very malignant nature, they did not offer the symptoms of hyperparathyroidism.

The first case of malignant tumor which did offer the symptoms of hyperparathyroidism or "functioning malignant tumor of the parathyroid" was reported upon by Wilder and Wellbrock in 1929 and was then included in the study by Alexander and co-workers. These authors also collected the other cases of this type given by Quick and Hunsberger, Sainton and Millot, Snell and Mayo, Petersma, Meyer, Rosi, and Ragins, Gentile, Skinner, and Ashburn, adding, as already mentioned, thirteen of their own cases of malignant hyperfunctioning parathyroid tumors. Meyer and Ragins published another case in 1943.

It seems worth while to subject the clinical picture as well as the development and the microscopic findings to a closer analysis.

Among the thirteen cases of Alexander, Pemberton, Kepler, and Broders, ten are referred to as malignant functioning parathyroid tumors (parathyroid adenocarcinoma grade 1, Broder's classification) and two as adenocarcinoma of the parathyroid gland, grade 3. As far as clinical data are available, neither local recurrences nor distant metastases were noted in any of the cases during the time of observation. Clinically, therefore, there was no indication of malignancy.

From a practical viewpoint the cases given by Gentile, Skinner, and Ashburn and by Meyer and Ragins are of special interest since here recurrences were accompanied by a re-appearance of hyperparathyroidism which, however, dis-

appeared again as soon as they were removed. Possibly similar cases of recurrent hyperparathyroidism are also due to malignancy.

Although the classification introduced by Alexander and co-workers promised to throw new light on our knowledge of hyperparathyroidism, it must be pointed out that the clinical development of these and other cases was only very rarely indicative of carcinoma. This is in accordance with the experience that hyperfunctioning endocrine organs in general only exceptionally develop malignant tumors.

From a practical viewpoint, therefore, clinical malignancy does not so far seem to play any important role in connection with hyperparathyroidism but it should be borne in mind that a clarification of microscopic conditions is of great importance regarding further developments.

Moreover, x-ray therapy in the treatment of malignant tumors was a failure (Meyer and Ragins, Quick and Hunsberger). As to nonmalignant tumors, results of x-ray treatment are contradictory (Merrit and McPeak, Cutler and Owen, Jacox, King, and Bailey). The latter authors reported an apparent regression of parathyroid hyperplasia after irradiation, and on autopsy no parathyroid changes could any longer be found.

DIFFERENTIAL DIAGNOSIS

In view of the great variety of clinical pictures and the very frequent deviation of biochemical findings which in well-determined cases are so clear-cut, and further in view of the abundance of osseous affections resembling the osseous type of hyperparathyroidism, the differential diagnosis offers a certain amount of difficulty.

As to the osseous affections resembling the osseous type of hyperparathyroidism, mention must be made of *osteodystrophy and osteofibrosis without parathyroid adenoma or hyperplasia.*

Localized Osteodystrophy.—Different types of localized osteodystrophy are osteitis fibrosa localisata, brown tumor, juvenile osteodystrophy, osteoclastoma, or bone cyst.

The differential diagnostic distinction or, to put it more appropriately the relationship between the osseous type of hyperparathyroidism, on the one hand, and localized or not generalized osteitis fibrosa or whatever its name may be, on the other, lies in the following facts:

(1) In the generalized type that is, in Recklinghausen's disease or the classical osseous type of hyperparathyroidism the skeleton shows certain changes consisting in cysts and brown tumors which, histologically, are in nothing distinguished from the localized type.

(2) In certain cases of Recklinghausen's disease the localized manifestations were so pronounced, clinically, that they occupied the chief role in the history and diverted attention from the essential disorder (Barr and Bulger, Snapper and Boere, Elmslie and co-workers [epulis], Churchill and Cope).

(3) In the opinion advanced by several authors, localized osteitis fibrosa may develop into the generalized type, this has proved incorrect particularly

in view of the fact that it has now been established that the two conditions arise from two completely different etiologic bases. In no case of osteitis fibrosa localisata were any signs of hyperparathyroidism noted nor was the calcium metabolism deranged (Mandl, 1926). The customary examinations and careful x-raying will prevent localized osteitis fibrosa, occurring as part of a generalized one, from being overlooked. The search in cases of this kind for a parathyroid adenoma or other parathyroid changes as it is often referred to in the literature but always with negative result (quoted from Weissenbach and Lièvre) is entirely without foundation.

(4) In cases apart from the strictly localized type of osteitis fibrosa there are those with multiple lesions scattered all over the skeleton. There are other cases in which all bones show cystic changes and eventually there are those with unilateral involvement of the entire skeleton on that side. Freund and Meffert refer to cases of this kind as nongeneralized fibrous osteodystrophy and give an account of seven out of a series of twenty-five patients with strictly localized disease, with extensive involvement (two with multiple localized lesions, two with diffuse monostotic lesions, and three with unilateral fibrous osteodystrophy). As it was seen from serum examinations and from further developments, these cases had nothing in common with the generalized type of the disease nor did they merge into it. None of the cases, moreover, offered any indication of parathyroid adenoma that would have produced hyperparathyroidism. In one of the cases of "unilateral" fibrous osteodystrophy the search for a parathyroid adenoma was also in vain.

It appears, therefore, that we are here dealing with a condition so far completely unclarified as to its nature which, by the way, had already received a similar name by Borak and Doll in 1934 in view of the fact that no parathyroid adenoma could be found (Mandl) (see Albright's syndrome).

Only Coenen (1937) mentioned the case of a 21-year-old girl with "unilateral Recklinghausen's disease" in whom a parathyroid adenoma was removed with permanent effect.

In 1926 I pointed out the difficulties with which the nomenclature meets in these cases.

Paget's Disease.—The relationship between Recklinghausen's disease (the classical type of osseous hyperparathyroidism) and Paget's disease is rather a close one for several reasons although we must point out from the beginning that Paget's disease is no manifestation of hyperparathyroidism and has nothing in common with that condition.

If, however, this question arises again and again, if confusions are common and the relationship between the two conditions is constantly referred to, this is preponderantly due to the fact that for a long time no histologic differences were found between Recklinghausen's and Paget's disease. In both, the bone marrow shows fibrosis and in both, at least in the opinion of certain authors (Lièvre), cysts and brown tumors (Looser) are encountered, although this idea was rejected by Snapper. It is, however, according to the results of latest research (Knaggs, Freund, and Schmorl), the so-called mosaic structure that

is today generally accepted as a characteristic feature of Paget's disease of bones that distinguishes the two conditions (see Snapper, 1943, Plate XX).

Clinically, the two conditions offer an entirely different aspect. In Paget's disease the patient's general condition is good and the bone deformities which may persist for years without causing pain hold the foreground. An increase in the size of the skull is often the very first symptom. Paget's disease occurs in patients at an advanced age and has practically never been noted before the fortieth year of life. Spontaneous fractures are rare. There is a monostotic as well as a generalized variety.

The classical picture of Paget's disease is fundamentally different from that of Recklinghausen's disease. Regarding biochemical findings, in Paget's disease, in contradistinction to Recklinghausen's disease, calcium and phosphorus are normal in the serum and urine, while the phosphatase values in the serum may be found increased in both (Kay).

Although, therefore, the comprehensive studies by Schmorl, Léri, Gutman, and Kasabach render it practically impossible to confuse the two conditions, in the development of hyperparathyroidism and in its treatment, Paget's disease plays a certain role.

1. To begin with, in atypical cases of Recklinghausen's disease the bones may here and there show traces of recalcification which may in the x-ray view give rise to confusion with Paget's disease. This holds particularly true (Weissenbach and Lièvre) of those cases in which the development is a slow one without other signs of hyperparathyroidism (pagetoid type).

2. Provided there is a possibility of spontaneous healing in Recklinghausen's disease, as held by certain authors (Oestling), this process of recovery can manifest itself in the radiogram only by sclerosation, a condition that, in conjunction with the still existent deformities, may give rise to confusion with Paget's disease.

3. In my first patient operated upon for Recklinghausen's disease the recalcification of the bones appearing in the course of the first few postoperative weeks and months after successful parathyroidectomy was interpreted by Kienböck in a way that made it probable that the case had not been one of Recklinghausen's but rather one of Paget's disease. This objection which proved entirely incorrect was even then refuted by me (1934). Today it is generally known and has been verified on numerous occasions that the process of recovery taking place in the bones after parathyroidectomy has nothing in common with Paget's disease. In 1941 attention was drawn again to this point by Couch and Robertson.

4. In spite of the many objections, certain authors continue to adhere to the view that there exists a relationship between Paget's disease and the parathyroid glands. This is held, for example, by Donati and by Hellström, who distinguished a special type of hyperparathyroidism which "simulates or is complicated by Paget's disease." Ballin even went so far as to advocate parathyroidectomy in the treatment of Paget's disease which, in his opinion, should be attributed to an excessive parathyroid activity, probably since he found a

definite parathyroid adenoma in one of his cases. Churchill and Cope pointed out, on the strength of another case reported by Walker, Irving, and Aub (quoted after Churchill and Cope, that coincidence of the two disorders was recorded and verified by radiographic and chemical findings. In any event this is a very rare exception.

Gutman and Parsons gave a very instructive synopsis of 150 cases of hyperparathyroidism and 146 of Paget's disease with enumeration of the various symptoms.

In this connection it should be pointed out that especially Schmorl, for autopsies in 190 cases of Paget's disease reported not a single one in which there was any indication of hyperactivity of the parathyroid glands. Similarly, Snapper reported two cases, Mandl three, and Churchill and Cope one of Paget's disease in which no adenoma of the parathyroid could be found on operation. It appears, therefore, that Paget's disease belongs to the category of osteofibroses without parathyroid hyperfunction and that it is not connected with parathyroid adenoma.

Albright's Syndrome.—Albright's syndrome consists of polycystic fibrous dysplasia with pigmentation of the skin associated with pubertas praecox in females, and similar conditions (Lichtenstein and Snapper).

In one of the first cases of this type, today generally known under the designation of Albright's syndrome and published for the first time by Albright in 1937, I had the opportunity of participating in the observation. I also performed an unsuccessful operation of this type. The case was then published by Borak and Doll in 1934. Since it is not known in the American literature an extract is given here:

The patient had had a vaginal hemorrhage when she was 10 years old which had persisted for several days and had recurred after three months. The abnormal development of the breasts and the pigmentation of the nipples was striking at that time. When she was 8 years of age there was hair on the mons pubis, and when she was 10, in the axillae. Height and weight, on the other hand, were not particularly abnormal. When she was 6 years of age, she sustained a spontaneous fracture of the left femur. A roentgenogram made on that occasion showed that the entire femur was changed. There was diffuse enlargement of the bone with thinning of the corticalis, decalcification, and a fracture in the subtrochanteric region. These fractures recurred at other places of the left thigh in 1932 and 1933. Healing was always satisfactory in simple plaster of Paris casts and left no callus. Apart from a waddling gait there were no particular functional disturbances.

Roentgenograms revealed that the entire skeleton including the spine, the ribs, and the left shoulder region contained the same changes as those noted in the left femur to a more or less extensive degree. The bones of the pelvis, moreover, showed a rather sharply outlined light patch, the size of a palm, just above the hip. Similar changes were found in the phalangeal and metacarpal bones, and in those of the left forearm and upper arm. At the occiput a bony swelling could be palpated. Qualitatively the bone changes were characterized by decalcification, bony swelling, and thinning of the corticalis in the long tubular bones while the short tubular bones and the occiput, although thickened, showed hyperostoses. The striking feature was the exclusive involvement of the left side of the body throughout a period of observation of four years.

In view of the high blood calcium (19.8 mg. per cent) and the excessive calcium elimination in the urine (42 mg. per day) a parathyroid tumor was searched for operatively (Mandl). On operation, a formation giving the impression of an enlarged parathyroid gland

was removed but was verified by histologic examination as consisting of purely thyroid tissue. The parathyroid glands themselves were normal. The operation had not, therefore, any objective effect, and four months later the patient had another spontaneous fracture of the femur while the calcium level of the blood remained permanently increased.

From the foregoing it can be seen that by 1934 I was able to ascertain that the syndrome was not connected with a parathyroid tumor. In the discussion taking place after Borak and Doll had presented the case, I pointed out that we were dealing with a separate syndrome which had nothing in common with hyperparathyroidism or Recklinghausen's disease.

In 1937, Albright, Butler, Hampton, and Smith reported upon five cases of that type to which Albright, Scoville, and Sulkowitch added another two in 1938. At that time it was clear that the syndrome, the etiology of which remains unclarified, had nothing in common with hyperparathyroidism and that any search for a parathyroid tumor or any operative manipulation on these lines is absurd.

Dockerty and co-workers (1944, 1945) gave a review of thirty-nine cases they collected from the literature with addition of six of their own observed at the Mayo Clinic. Nothing new could be said about the etiology which remains obscure (Mondor, Ducroquet, Leger, and Laurence, Braid, Robson and Todd, Summerfeldt and Brown, Neller.

Other varieties of the disorder are referred to in publications by McCune and Bruch giving an account of cases including, in addition to the previously mentioned symptoms of fibrous osteodystrophy with pathologic pigmentation of the skin and pubertas praecox, the signs of hyperthyroidism. One of the cases, described by Sternberg and Joseph, is particularly interesting in view of the post-mortem which could be performed and during which especially the endocrine organs were very carefully studied. For our considerations it is worthy to note that no parathyroid changes were found. Possibly we were dealing with a certain variety of Albright's syndrome, because comparatively often more or less distinct manifestations of hyperthyroidism are met with in this disease (cases reported by Musser and Barnwell, Gaupp, Goldhammer).

The laboratory data, by the way, are normal in this condition, regarding calcium and phosphorus in the blood and urine, while the phosphatase may be increased.

It is, therefore, rather astonishing that in twenty of the cases reviewed by Dockerty and co-workers a search was made for parathyroid tumors, although it was always unsuccessful.

The osseous involvement is very frequently unilateral, and renal complications as they are customary in hyperparathyroidism are almost never encountered.

A similar condition was referred to by Lichtenstein in 1938 as "polyostotic fibrous dysplasia of bone," and later, in 1942, in a publication by Lichtenstein and Jaffe as "fibrous dysplasia of bone," a condition affecting one, several or many bones, the graver cases of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism, or other extraskeletal abnormalities.

In 1942, these authors gave an account of twenty-three cases and it is pointed out that the condition is identical with that described by Goldhammer, Borak and Doll, McCune and Bruch and Albright with the only exception being that the osseous as well as the extraskeletal manifestations may vary in degree. In their opinion, approximately fifty-three different designations have been used for the same condition in the course of the years (osteitis fibrosa, osteodystrophia fibrosa, focal, unilateral, disseminated, fibrocystic disease of the bone, a form of Recklinghausen, regional, or unilateral Recklinghausen). Lichtenstein and Jaffe in their statistics give a complete list of Albright's 90 cases:

In 15 out of 87, the disease showed monostotic involvement, while in 17 out of 87 several bones were attacked. In 12 of these 17 an entire limb was involved. In 29 out of 87 cases the skeletal involvement was more extensive but predominantly one-sided while in the remaining 26 very many bones were affected. In 32 out of 90 cases there was pigmentation of the skin and in this respect there was no difference between the two sexes. No more than 20 cases (out of a total of 90) showed signs of endocrine dysfunction (hyperthyroidism, premature sexual maturation, premature skeletal growth).

Eventually, Snapper (in 1943) referred to the same syndrome as lipoid granulomatosis of the bones without craniohypophyseal localization and reported several cases of this type. As to therapy, aluminum acetate treatment advocated by Helfet seems to have proved its value.

Cases of polycystic fibroid dysplasia have also been repeatedly described (Horwitz and Cantarow, Cherry, Moehlig and Schreiber) with varying localization. The case reported upon by Moehlig and Schreiber was of a large bone tumor of the skull with unilateral involvement of the skeleton of the extremities. An interesting feature of the case (a boy 16 years of age) was, moreover, the coexisting hypopituitarism, manifested by gynecomastia, absence of beard and axillary hair, and puerile type of voice.

Renal Osteodystrophy.—Various renal disorders may give rise, in contradistinction to the primary renal type of hyperparathyroidism, to a so-called secondary hyperplasia of the parathyroid tissue. Reference to this form of the disease has been made before. They furnish the evidence that for certain osseous affections accompanied by a general parathyroid hyperplasia, Erdheim's original theory still holds true.

This renal osteodystrophy has been observed in children and adults alike. It is also found as an accompaniment of chronic interstitial nephritis in adults especially if there is simultaneous acidosis which is, by a number of authors, held responsible for the osseous changes (Mach and Rutishauser, Guye and Rutishauser, and others).

This condition in which the renal disturbance usually predominates sometimes is characterized by osteoporosis, as a rule, however, by osteodystrophy. The parathyroid glands need not necessarily be enlarged and may be completely normal.

For the surgeon it is important to note that, in contrast to findings in hyperparathyroidism, the blood calcium is low and the blood phosphorus high (see Table IV).

Various Other Osseous Affections.—To the category of other osseous affections belongs for example, the case published by me in 1935 (Case 6). Here the x-ray aspect and the existing hypercalcemia were suggestive of osseous hyperparathyroidism. But on operation, although the entire region was carefully explored, no adenoma could be detected. An enlarged parathyroid gland was removed. The calcium level of the serum dropped but the osseous symptoms increased in intensity. Only later was a diagnosis made of carcinosis of the skeleton. The calcium in the serum again rose to 16 mg. per cent. On autopsy, a carcinoma of the prostate was found.

Another interesting case was reported by Rahm. The x-ray findings in a 20-year-old patient with generalized cyst formation were "typical" of Recklinghausen's disease. In 1932, an unsuccessful operation was performed for parathyroid adenoma but only a lobe of the thyroid gland was removed. The blood calcium was 12.5 mg. per cent and dropped to 8.1 to 10.7 mg. per cent after the operation, while the blood phosphorus increased to 3.7 to 6.4 mg. per cent. In 1938, the patient developed a tumor in the gluteal region. Later he died from pleural empyema and, on autopsy, hemangiomatosis of the skeleton was found with involvement of the soft parts.

The high phosphorus values are not exceptional, particularly since Rahm himself in 1938 described an osseous parathyroidism with a phosphorus level of 6.2 mg. per cent presenting a typical parathyroid adenoma on operation.

However, if the calcium and phosphorus values are indecisive and x-ray findings are obscure, one should not undertake operation before making a *biopsy* of the bone at an easily accessible site. In a case described by Bretschger the diagnosis was established only in this way.

A rarer differential-diagnostic problem was presented by the following case reported by Albright, Burnett, Cope, and Parson:

The patient, a boy 14 years of age, had a spontaneous fracture of the femur through solitary bone cyst (plaster cast). In the course of time he developed anorexia, vomiting, and hypercalcemia (14.6 mg. per cent), while the serum phosphorus and phosphatase were normal. X-ray views showed decalcification of the immobilized part of the skeleton without involvement of other bones.

Since there was also hypercalciuria, an exploration of the parathyroids was twice attempted but neither an adenoma nor hyperplasia was found. The patient was mobilized and activity and weight-bearing were forced. After one month the serum calcium was normal, anorexia and vomiting had ceased, and the renal function was normal. The patient had, therefore, completely recovered.

Similar cases have been referred to by Howard and Cuthbertson.

The list of the different varieties might be continued ad libitum (myelomatosis and carcinosis of the skeleton have been referred to under Primary and Secondary Hyperparathyroidism).

PARATHYROIDECTOMY

The method of choice in the treatment of primary hyperparathyroidism is parathyroidectomy.

It is obvious that if possible it should be tried, prior to operation, to clarify the localization of the parathyroid tumor. This can be done by palpation and also by x-raying.

Prior to and during the operation the decisive point is whether one is dealing with a normal or a pathologic situation. It is, further, of importance to be acquainted with the aspect of normal parathyroids and to know when the organ should be regarded as enlarged. The reduction of parathyroid substance requires technique other than the removal of one or two distinct tumors.

During the operation it is of greatest importance to ascertain whether the tissue that has been removed is actually that of the parathyroids.

Finally, the importance of forestalling postoperative tetany cannot be sufficiently stressed.

Since the adoption of the operative method devised by Churchill and Cope in diffuse hyperplasia (to be described later) the weight of the parathyroid tissue has also become important to the surgeon. According to Pappenheimer and Wilens one normal gland weighs 0.027 to 0.032 Gm. In a large-scale study by Gilmour and Martin comprising 527 cases, among which 301 were normal, the maximum weight of the normal organ was established as being 120.8 mg. in the male, 139.7 mg. in the female subject. In the "endocrine" group and in the "renal" group the weight increased to nearly three times the normal one (the entire gland being weighed). The weight of the "parenchyma" alone is not so much increased.

For the surgeon the pathologic localizations are of greatest significance. Among them the most important are (1) in the vicinity of the common carotid, (2) in the vicinity of the phrenic nerve, (3) in the anterior mediastinum, (4) in the posterior mediastinum, (5) within the thyroid tissue.

It is clear that parathyroid tumors may vary in localization in accordance with this outlined localization of the normal organ (to be discussed).

Parathyroidectomy for Parathyroid Adenoma.—Palpation of a parathyroid tumor is only very exceptionally possible, in Snapper's opinion in no more than 5 to 10 per cent of cases. Usually, however, palpatory findings are misleading and what is palpated is often a thyroid lobe. Very exceptionally a silent tumor has been found on palpation while other signs of hyperparathyroidism were absent (Barker and Brines). Alexander, Kepler, Pemberton, and Broders were more successful. In their series of fourteen cases of parathyroid tumor, palpatory findings were positive in three (21.4 per cent). In two cases the parathyroid tumors had caused upward displacement of the thyroid, thus providing positive although misleading palpatory findings.

If palpation is negative or undecisive it can today be demanded that an exact roentgen examination precede the operation and that it be ascertained whether possibly the tumor lies in the anterior or posterior mediastinum where it may cause displacement of the trachea or esophagus. Cases in which a shadow

was found in the anterior mediastinum, a calcified tumor of that site, kinking of the esophagus, or posterior displacement of the trachea have been referred to by Bergstrand, Brown, Goldmann and Smyth, Snell (quoted by Snapper, 1943), Alexander and associates, Cope, Lahey, and Miller. Misinterpretation of such mediastinal shadows have also occurred. Thus, for example, Vilvandré refered to a parathyroid tumor as a mediastinal tumor of an ill-defined nature, and confusion with aneurysm of the innominate artery or substernal goiter were also reported (Hirsch). On the other hand, in a case reported by Anderson (quoted by Snapper) compression of the trachea on the right and of the esophagus on the left apparent in the roentgenogram could be diagnosed as due to bilateral adenoma which could be verified by operation.

In spite of these interesting findings it must be admitted, however, that in the majority of cases the localization of the tumor is not realized before operation and that usually a thorough search has to be made. The salient point of the operation is this search, and that, first of all, the normal sites are explored goes without explanation.

Up to the year 1933, I collected sixty cases of parathyroidectomy from the literature and out of fifty-five, in which the localization was mentioned the site of the tumor was normal in forty-three (see Table V).

TABLE V

LOCALIZATION	NUMBER OF CASES
Right	
Above	5
Below	12
Above and below	1
Left	
Above	1
Below	18

In six cases no special mention was made of the localization. From this tabulation a distinct preference appears of the lower parathyroids.

Twelve of the cases presented by abnormal localization, as shown in Table VI.

TABLE VI

LOCALIZATION	NUMBER OF CASES	AUTHOR
Intrathyroidal	4	Gordon-Taylor and Handley, Wichmann, Lahey, and Gold
Underneath the left clavicle	1	Barr, Bulger, and Dixon
In the carotid triangle	2	Wilder, William, and Wellbroek
Substernally	3	May and Lièvre, Walton, Hunter, and Mandl
Between esophagus and trachea	1	Walton and Hunter
Behind the trachea	1	Hunter

Therefore, in nearly 25 per cent of the cases the localization was an abnormal one. In the meantime the knowledge of this misplacement of parathyroid tumors has become rather general, although it may happen that the tumor is not found at all. Apart from the fact that I was unable to detect a parathyroid tumor, an experience of this kind has led a number of surgeons to far-reaching conclusions regarding the value of this operation in general.

Let us compare the state of affairs in an operative respect with these statements.

It was reported by Alexander, Pemberton, Kepler, and Broders that nine among fourteen tumors were found on the right side while only five were on the left.

> In one case the tumor was within the right lobe of the thyroid gland, was nodular and extended into the superior mediastinum. In the other 13 cases the tumor was outside the thyroid parenchyma . . . in 7 cases the tumor was situated at the lower pole of the corresponding thyroid lobe. In 3 of these cases the tumor projected through the superior into the posterior mediastinum. In one of the latter cases the tumor lay behind the trachea and esophagus. In 4 instances the tumor lay behind the corresponding lobe of the thyroid gland midway between the lower and upper poles, while in one case the tumor was found behind the upper poles. In another case the tumor lay in the left anterior mediastinum and could be removed only after the sternum had been split.

In four out of fourteen cases, therefore, the tumors were in the mediastinum, one time in the anterior and three times in the posterior one. All the tumors could be removed operatively.

Krausz, in 1939, reviewed five cases of hyperparathyroidism. Three of these patients were cured. In one who died, two tumors had been present of which, however, only one had been found on operation. In another the tumor lay behind the esophagus and could not be detected on operation. Among four tumors only one was found at a normal site. Krausz, therefore emphasized the difficulties of operative therapy.

The more diversified and the larger the series of patients the more important is it for the surgeon to have a wide experience. Thus, Cope reported in 1941 that at the Massachusetts General Hospital in Boston, up to the year 1941, sixty cases of hyperparathyroidism had been observed. Fifty-eight times the diagnosis was established during the operation and only twice on autopsy. There were fifty-four adenomas and in only six cases was primary hyperplasia found. Among the fifty-four adenomas, there were two tumors in four cases, and one in the remainder, so that there was a total of fifty-eight adenomas. Of these, eleven were in the anterior, five in the posterior mediastinum, and the remainder in the neck region.

Cope's number of mediastinal adenomas (sixteen out of fifty-eight) was, therefore, particularly great so that he undertook the important task of studying the reasons for the presence of the parathyroid tumors in the mediastinum (embryologic descent and displacement from the neck into the mediastinum). Walton was the first to perform an operation on such a descending parathyroid tumor.

Cope devised a special method for the detection of these tumors. He divided the operation into two stages, during the first of which the neck region, posterior mediastinum, esophagus, and trachea are explored. During the second, in case the tumor has not yet been detected by the first procedure, the sternum from the manubrium up to the level of the third interspace is split.

This method has already been used by Gordon-Taylor who succeeded in removing a parathyroid tumor from the anterior mediastinum by transsternal

approach (Gordon-Taylor and Handley). Cope found it necessary, however, to apply this method systematically in view of the great number of his mediastinal cases and the impossibility to reach the tumors from an incision at the neck which is very instructively illustrated by the sketch attached to Cope's article.

The recognition of intrathyroid tumors is fraught with considerable difficulty. Lahey operated upon three patients with this difficulty. No rules can be laid down as to how to conduct the search for these tumors. The unilateral "blind" thyroidectomy, in case the adenoma is not found, as a method of choice does not, in my opinion, offer a sufficient degree of certainty.

In the cases published by Schlesinger and Gold, Couch and Robertson and that by Bauer, intrathyroidal parathyroid adenomas were present.

Secondary Operations.—Although with advancing experience and increased thoroughness of the operation (see Cope) the number of secondary operations has surely decreased, they still play an important role in the history of parathyroidectomy as well as in actual fact. If after failure to detect an adenoma the operation is discontinued, if a tumor mass is removed which on microscopic examination does not prove to be a parathyroid tumor, or if, after an unsuccessful search for an adenoma, normal parathyroid tissue has been removed, in the majority of cases the patients are *not* improved and the surgeon sees himself confronted with the necessity of proceeding to another operation.

The classical case of Dubois, which was the first in which the presence of hyperparathyroidism was suspected and a search instituted for a parathyroid tumor, ran a very characteristic course in this respect (Hannon, Shorr, McClellan, and Dubois). During the first operation two normal parathyroid glands were extirpated while no tumor was found. The improvement the patient showed after the operation remains, as a matter of fact, inexplicable (high calcium diet). In the course of time, however, renal damage with stone formation became more and more pronounced. It was only during the seventh operation that a parathyroid tumor was detected in the anterior mediastinum. Churchill and Cope performed only subtotal resection of the tumor and transferred the rest from the mediastinum to the neck region. This ingenious idea to avoid tetany in the patient who had already lost sufficient parathyroid tissue, however, was not awarded by success. A stenosing calculus of the ureter had to be removed and the patient, who was already in a very poor condition, died twenty-six hours after the operation.

Up to the year 1936, Churchill and Cope's thirty cases included five of secondary or repeated operations. The interval between the first and second or third operation was, including the famous case of Captain Martell on whom seven operations had been performed, five to twelve months.

Failure to achieve success by the first operation is due to the fact that usually normal parathyroids, thyroid tissue, or thymus is removed. During the last operation, the successful one, the responsible parathyroid adenoma was three times in the anterior mediastinum, once retroesophageally and once behind the right thyroid lobe. Again Churchill and Cope proceeded in such a way as to avoid serious tetany where parathyroid tissue had been removed previously, by performing subtotal resection.

From the literature it appears that in primary hyperparathyroidism due to parathyroid tumor the extirpation of normal parathyroid tissue is of no avail and since the patient is not impoved, a secondary operation usually must follow and eventually when the responsible parathyroid tumor is removed the likelihood that postoperative tetany may develop is all the greater. The contrary view I once held, and which has rightly been criticized by Snapper, I hope thus to have corrected.

The Technique of Parathyroidectomy in the Presence of Multiple Tumors or Hyperplasia of the Entire Parathyroid Tissue.—It is also to Churchill and Cope that we owe the technical directions for cases of parathyroidectomy with multiple tumors or hyperplasia of the parathyroid tissue. These authors were the first (1934) to recognize the existence of multiple tumors or diffuse hyperplasia of the parathyroid tissue. They were followed in short succession by publications on six cases of this type from the Boston school.

In the first case two, hyperplastic parathyroid glands were extirpated during the first operation, and during a second a subtotal resection was made on the third enlarged gland. The fourth parathyroid could not be discovered. After the operation this patient still showed a mild tendency to hyperparathyroidism.

In the second case (Case 16, Churchill and Cope) only two hypertrophic parathyroid glands were extirpated weighing 15.6 Gm.

In the following case actual diffuse hyperplasia of all parathyroids is described and all four of them were exposed. Three were totally removed, while on the fourth a subtotal resection was performed. The extirpated tissue weighed 3.4 Gm.

In three further cases of diffuse parathyroid hyperplasia the procedure was as follows (Case 23 of Churchill and Cope):

> The patient had the typical aspect of skeletal and renal manifestations. A biopsy was made of a suspicious lesion which, on x-ray examination, showed atypical chondrosarcoma. On repeated examination the urine showed a small amount of Bence-Jones protein body. However, calcium in the serum was increased and phosphorus was very low. During the operation (July 12, 1934) all four parathyroids were found hypertrophied: right inferior 8 by 6.3 mm.; left superior 3 by 1.7 by 0.8 cm.; left inferior 1.1 by 0.6 by 0.3 cm.; right superior 7 by 4 mm. The first three glands mentioned were extirpated while from the fourth a biopsy specimen was taken. The tissue removed weighed 2.47 Gm. There were no signs of tetany. After the operation calcium and phosphorus values in the serum soon returned to normal and the patient recovered rapidly.
>
> Microscopically, the hyperplasia was of the type characterized by water-clear cells.

The procedure adopted by Churchill and Cope was similar in their two other cases. The three glands in which hyperplasia was of the highest degree were totally removed and on the fourth a subtotal excision was performed. The total weight of the tissue removed was 6.8 Gm. and 11.2 Gm., respectively.

The first patient developed a transient tetany while the second remained normal. Calcium and phosphorus values of the serum returned to normal very soon after the operation in both cases. The hyperplasia was in both types characterized by water-clear cells.

In broad outline this is the operative technique in the presence of diffuse hyperplasia. It was summed up by Churchill in 1937 in his "Principles of

Parathyroid Surgery'' and by Cope in ''The Surgery of Subtotal Parathyroidectomy.'' From practical experience it appears that the procedure advocated by Churchill and Cope is the right one.

Tetany.—In view of the fact that tetany (hypoparathyroidism) is a very serious postoperative complication it seems worth while to discuss this point in greater detail. In the third patient I operated upon, in 1933, a very peculiar type of late tetany with mental disturbances was noted which was, no doubt, the reason why the patient died. Such ''confusional states'' have been referred to elsewhere (Ask-Upmark, Wanke) and are beyond any doubt connected with the existent tetany. Among fifty-five patients operated upon up to 1932, I found postoperative tetany in nine, five of the patients recovering (Hunter, Snapper, Gold, Elmslie and associates), and four dying either during or immediately after the operation (Beck, Wanke, Ask-Upmark, Mandl). It was particularly the case reported upon by Beck in 1928 that, two years after the first successful operation, contributed much to discrediting the operative method. As I was able to ascertain, in several of the cases an excessive amount of parathyroid tissue had been removed, frequently normal and abnormal tissue together.

Up to 1936, McClure reported 125 cases of hypoparathyroidism he had found in the literature in which an adenoma had been extirpated in toto or in part. At the time when he made his report, eleven patients had died after the operation, seven with signs of hypoparathyroidism, of whom three had succumbed to this complication.

The same author described a case of tetany developing after extirpation of a parathyroid adenoma because of hyperparathyroidism, which is the first case of this type published in America (Wilder, Camp, Robertson, and Adams). McClure added one of his own cases, in which the patient died, four months after parathyroidectomy, from tetany.

A renewed perusal of the literature, however, shows that neither the statement I made in 1933 nor the view held by McClure is in conformity with actual facts and that tetany certainly appears much more frequently after operation for hyperparathyroidism, although it is now possible by various measures (to be discussed) to forestall fatal tetany. Thus, for example, among the first eighteen cases reported upon by Lièvre in 1932 nearly 50 per cent of the patients developed tetanic manifestations and Braine (1935) even reported tetany in 67 per cent of all operations for hyperparathyroidism. From more recent publications it appears that it was, first of all, the Boston group that approached the study of the problem of how to avoid postoperative tetany and introduced a special operative method for this purpose (''Conservative Surgery,'' Churchill and Cope). It appears, therefore, that the development of postoperative tetany after operation for hyperparathyroidism is generally feared. The second group of authors taking up the study of this question on a larger scale (Mayo Clinic) have now in their latest series of observations, published figures (Keating and Cook) which are of greatest significance for the understanding of the problem. While Churchill and Cope were guided, first of all, by the wish to reduce the parathyroid tissue and made important con-

tributions to this end, Keating and Cook in their recent series of twenty-five cases of hyperparathyroidism found that in 50 per cent of cases tetany developed in all three groups. Within the three groups, the distribution was six times in the group of classic bone disease. In this category comprising seven cases, it appears that there was only one with no manifestations of tetany. It must be pointed out, however, that among these six there was only one case of a severe character. Of nine cases of the second category, minimal bone disease tetany was noted only twice, while in the third group of eight cases without evident bone disease, tetany occurred only four times. Regarding the frequency and severity of this complication, the first group is certainly leading and Albright's old theory, which had already been confirmed by Jaffe and Bodansky, implying that there exists a relationship between tetany and the degree of bone changes or the level of the alkaline phosphatase values (danger limit, 14 to 20 units), seems to find confirmation (Albright).

Another important point is whether or not there exists a difference between hypoparathyroidism with tetany after operation for goiter and the type developing after operations for hyperparathyroidism. No doubt, after an ordinary goiter operation tetany is much rarer than after operation for hyperparathyroidism.

Swiss authors (Clairmont) quoted 1½ per 1,000 for Bern and 4 per 1,000 for Zurich, which is similar to American figures (Crotti, six times among 7,500 operations). It appears, therefore, that with improving technique postoperative tetany no longer plays a major role. Swinton gave 0.2 per cent for 15,552 thyroid operations of the Lahey Clinic.

Conditions are different where hyperparathyroidism is concerned. Here operation consists in at least the removal of excessively functioning parathyroid tissue, and the likelihood for hypoparathyroidism to develop is, therefore, far greater than after an ordinary goiter operation.

As a rule, after operation for hyperparathyroidism the originally high blood calcium drops abruptly, frequently below the tetanic limit (7 mg. per cent). Two other factors are likely to reduce the activity of the remaining parathyroid tissue or even to abolish it altogether. First of all, we know nothing about the state of activity of the normal parathyroids remaining in the organism. Even if they are of normal size, they may be inactive after the entire activity has been taken over by the adenoma removed (Mandl). So far nothing is known about the function of this normal parathyroid tissue prior to and after the extirpation of a hyperactive adenoma. Account should be taken further of the calcium hunger of the osteoporotic skeleton after operation on a parathyroid adenoma (Snapper), likely to intensify the hypoparathyroid tendency: "After the operation the decalcified skeleton absorbs the calcium from the plasma with so much avidity that the calcium current which, before the operation, went from skeleton to blood, is reversed. The quantities of calcium which are now withdrawn from the blood plasma are so large that hypocalcemia and tetany result. Even the presence of three remaining normal parathyroids is then not sufficient to keep the calcium metabolism in its normal pathways." On the other hand, if tetany develops after an operation for

primary diffuse hyperplasia of parathyroid tissue, the explanation is rather simple: it occurs as a result of extirpation of excessive amounts of parathyroid tissue. In cases of this type the prevention of tetany is a technical question (Churchill and Cope).

A perusal of the literature concerning postoperative tetany after operation for hyperparathyroidism yields no indication of a relationship between a high preoperative calcium value in the blood and the postoperative hypoparathyroidism.

Jaffe and Bodansky pointed out that the more intense the bone changes the higher the phosphatase and the higher and the more difficult it is to control hypocalcemia following a successful parathyroidectomy, in other words, the severer postoperative tetany. The authors explain it by the depletion of the skeleton "which represents a sort of vacuum which greedily sucks in for repair considerable circulating calcium, thus tending to create a prolonged postoperative hypocalcemia."

This biochemical explanation for the theory of the calcium hunger of the skeleton does not apply to all cases. On the other hand, tetany is not necessarily always accompanied by a low calcium level in the serum. I saw cases of tetany with 11 to 12 mg. per cent of calcium and others which with a calcium level of 5 to 6 mg. per cent developed no tetany.

On the whole, it may, therefore, be said that the occurrence of postoperative tetany cannot be foretold with certainty from preoperative findings and that an adequate amount of caution during the operation is often able to prevent it. It is for this reason that Churchill and Cope (1936) suggested removing part of the adenoma only if a postoperative tetany had to be feared and moving the remainder of the adenoma superficially into the neck region so that it might be removed easily in case the operation was not completely successful. This "conservative surgery" should be adopted, according to Churchill and Cope, (a) if the phosphatase value is higher than 14 Bodansky units, (b) in the presence of sepsis and general debility, (c) in renal dysfunction since in that case tetany is more difficult to control, (d) in an "unknown status" of the normal parathyroid glands as in secondary operations, (e) in an "unknown status" of the other parathyroids when dealing with multiple adenomas.

Similar ideas were expressed by Albert at the International Congress of Surgeons in 1935.

Measures to control tetany are: (1) administration of calcium per os or intravenously, (2) administration of vitamin D, (3) administration of parathyroid extract, (4) administration of A. T. 10 (dihydrotachysterol, Holtz, 1933), and (5) implantation of parathyroid tissue.

No detailed account can be given here of therapy. It should only be mentioned that the use of parathyroid extract is frequently followed by immunity to this treatment so that progressively increasing doses are necessary to maintain a normal calcium balance. It may even occur that intolerance to parathyroid extract develops (Aub, Wilder, Camp and Ochsner, Robertson and Adams, McClure, and Clairmont).

A considerable improvement of tetany therapy was the discovery by Holtz of A. T. 10 which is synthesized from ergostetrine. Independent of the original level it specifically increases the serum calcium. The effect does not set in before the lapse of twenty-four to forty-eight hours and constant checkup is necessary to avoid severe hypercalcemia.

A detailed report on this preparation was given by Bauer at the International Congress of Surgeons in 1935, and the indication, the shortcomings, and the danger of its use discussed. The difference between this method of treatment and that with parathormone is shown in Table VII.

TABLE VII

	PARATHORMONE	A. T. 10
Administration	Parenteral	Peroral
Effect	Immediate, rapidly subsiding	After 2 to 3 days, persistent
Dosage	1 to 2 times per day	Once a week
Serum calcium	Increasing, fluctuating	Increasing, constant
During acute attack	Immediate effect	No effect

Although A. T. 10 is of no avail during an acute attack, it is certainly very effective in chronic cases (Swinton, Brunner). Ineffectiveness of A. T. 10 has recently been reported (Stahl), a fact that was corroborated by Holtz.

There are authors who advocate, in cases of a chronic type, recourse to the old method of transplantation of parathyroid tissue (Braine and Rivoire, Mason and Warren).

RESULTS OF OPERATION

After the parathyroid tumor or the two tumors or, in the presence of diffuse hyperplasia, a sufficiently large amount of parathyroid tissue has been removed, the result of the operation manifests itself very rapidly. Snapper in his first case, similar to my first case, was able to ascertain an effect of the operation as soon as twenty-four hours after. Goldmann gave an account of a case in which after parathyroidectomy the preoperative calcium level of 19 mg. per cent dropped to 10.5 mg. per cent within six hours. This progressive improvement is in the subsequent few days threatened only by an intervening tetany and later by complications of the urogenital tract. The condition of the bones progressively improves during the first few months and the majority of authors report recalcification of the skeleton.

This much-discussed development of my first operation, in which the disease recurred after a complete cure of six years, gave rise to the anxious question as to whether the operation was of any permanent value at all and whether the other patients operated upon in the meantime were not threatened by a similar fate after an initial success. Today we are in a position to say that, fortunately, this fear was unfounded. Although the majority of authors still devote the greatest part of their attention to a further study of the disease and the diagnostic and technical possibilities, giving little information on the permanent results after operation, a number of data are available. Thus, for example, Snapper reported that his first patient died ten years after successful operation from coronary thrombosis, while the second was still in

a satisfactory condition after nine years (1939), and the third, operated upon in 1934, was in an excellent condition in 1940.

Coryn's patient, after four years was in so satisfactory a condition that osteotomy for the correction of deformity could be performed.

In a case reported by Wichmann the condition was still good after eight years. In several cases of Alexander, Pemberton, Kepler, and Broders the case reports published in 1944 to some extent include the results after an appreciable follow-up period. One patient (Case 1) operated upon in 1929 died in 1940 from esophageal carcinoma; the second (Case 2) operated upon in 1930 was still healthy after six years. For the other cases no follow-up data are given.

McClure and Lam, reported upon "End Results in the Treatment of Hyperparathyroidism." Five of their six patients submitted to operation. One of the patients operated upon died four months after the operation in a state of hypoparathyroidism, while the other four, whose conditions were followed very carefully for from four to eight years, are referred to by the author as normal individuals.

Himmelmann's patient was still healthy after four years and that of Laewen after two years. A patient reported upon by Rosenbach was still cured after eight years.

These data may suffice to demonstrate that the patients had fully recovered and that the operation had been of permanent value.

Although it is with great satisfaction that we may view the results of the development of hyperparathyroidism research during the past twenty years, a number of questions are still open and further studies will find a wide and fruitful field.*

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*The interrelationship between hyperparathyroidism and disturbances of other endocrine organs could just as little be discussed as the indications for and results of parathyroidectomy in other disorders.

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Book Reviews

Peripheral Nerve Injuries: Principles of Diagnosis. By Captain Webb Haymaker, M.C., A.U.S., Army Institute of Pathology, and Major Barnes Woodhall, M.C., A.U.S., Chief Neurological Section, Walter Reed General Hospital, Washington, D. C. Pp. 227, with 225 illustrations. Philadelphia, 1945, W. B. Saunders Company.

This little book is most valuable because of the manner in which it presents material rather than because it contains new information.

Many simple line drawings and good photography simplify the anatomy of nerve injuries and the tests for loss of nerve function. A very admirable feature is the sensory deficit depicted on the photograph or on a line drawing which accompanies the photograph. One not familiar with the anatomic detail of nerve injuries will find it possible to comprehend the anatomy of these injuries with a minimum of effort through the use of this book.

It should be a very useful volume for every practitioner who has occasion to examine for, or treat, nerve injury.

Anesthesia in General Practice. By Stuart C. Cullen, M.D., Head of Division of Anesthesiology, Department of Surgery, State University of Iowa Hospitals; Associate Professor of Surgery (Anesthesiology), State University of Iowa College of Medicine. With a Foreword by Frank R. Peterson, M.D., Professor and Head of the Department of Surgery, State University of Iowa College of Medicine. Pp. 260, with illustrations. Chicago, 1946. The Year Book Publishers, Inc. $3.50.

It is always a pleasure to read a book of this caliber. Dr. Cullen has the skill and ability to write both authoritatively and clearly as well as concisely. This book contains material which should recommend it not only to students of anesthesiology but to others as well. The chapter on preanesthetic medication might well be used as a basis for interns, and surgeons, too, who are called upon to order for patients preoperatively in hospitals where this duty is not taken care of by the department of anesthesiology. The chapter dealing with ways and means of maintaining an adequate airway in unconscious patients might very well be made required reading for all personnel who have entrusted to them the care and responsibility of the unconscious patient. This, of course, includes nurses.

The book is small and easily carried. The paper is good and the printing excellent. It is well bound. It is recommended without any reservations.

The Peripheral Circulation in Health and Disease. A Study in Clinical Science. By Robert L. Richards, M.D., with a foreword by J. R. Learmonth, C.B.E., Ch.M., F.R.C.S.E. Pp. 153, with 104 illustrations. Edinburgh, 1946, E. & S. Livingstone.

This 153 page monograph on the peripheral circulation covers in an admirable way the fundamental physiology of regulation of vascular tone in health and its pathologic variations in the common types of arterial disease in the extremities. Of particular interest are the discussions of nervous and local control of the peripheral vessels in Raynaud's disease, other conditions which give rise to the Raynaud phenomenon, and the description of circulatory abnormalities which are found after complete or partial injuries of the peripheral nerves. There is also a valuable chapter on the circulatory disturbances encountered after exposure to cold, particularly the wartime syndrome of immersion foot, which was studied so carefully by the Edinburgh school.

The book contains an excellent description of the methods of study for estimating the value of sympathectomy and the physiologic importance of the surgeon's interrupting the sympathetic pathway in its upper or preganglionic neurone. There are over 100 figures, of which the illustrations of temperature gradients observed in various forms of vascular disease and thermal variations following different types of nerve injury are of especial interest. This is a book written by a medical man trained in the school of critical clinical observation which was developed in Britain by Sir Thomas Lewis. Its exponents in England and Scotland have turned out a great number of papers of exceeding interest during the past decade—work which Dr. Richards has contributed to in person and has reviewed in a lucid, critical style. The monograph will appeal particularly to American readers on this score.

Hey Groves' Synopsis of Surgery. Edited by Cecil P. G. Wakeley, C.B., D.Sc., King's College Hospital, London. Pp. 632, with 195 illustrations. Baltimore, 1945, Williams & Wilkins Company. $6.

The fact that this textbook is now in its twelfth edition indicates that it has found a useful and popular place in the student's and practicing physician's library.

This edition, revised by Cecil P. G. Wakeley, maintains the high caliber of its predecessors and brings up to date many of the newer advances in surgery. The use of the sulfonamides and penicillin in the treatments of wounds and infections is discussed fully. Modern methods of radium therapy have been incorporated while some of the old amputation methods which are no longer in use have been omitted.

However, in an effort to be brief, this synopsis like all other synopses, loses its effectiveness as a teaching text. A good deal of important information is either omitted or mentioned so briefly that its importance is not properly stressed. As a typical example of this, the author of the section on empyema advised open drainage by resection of the eighth rib in the midaxillary or the ninth rib in the scapular line without mentioning the need for stabilization of the mediastinum prior to drainage or the advisability of obtainng a roentgenogram of the chest for localization of the empyema. In the chapter on the diseases of veins, no mention is made of phlebothrombosis as a separate entity from thrombophlebitis. Nor is there any comment, in the treatment of thrombophlebitis, on the use of sympathetic block, ligation of the vein, or anticoagulants. Finally, little or no information is given to the most important phases of preoperative and postoperative care of the surgical patient.

However, there is a great deal of information presented compactly. It will perhaps be used to the best advantage by the student or practicing physician in conjunction with some larger standard textbook of surgery.

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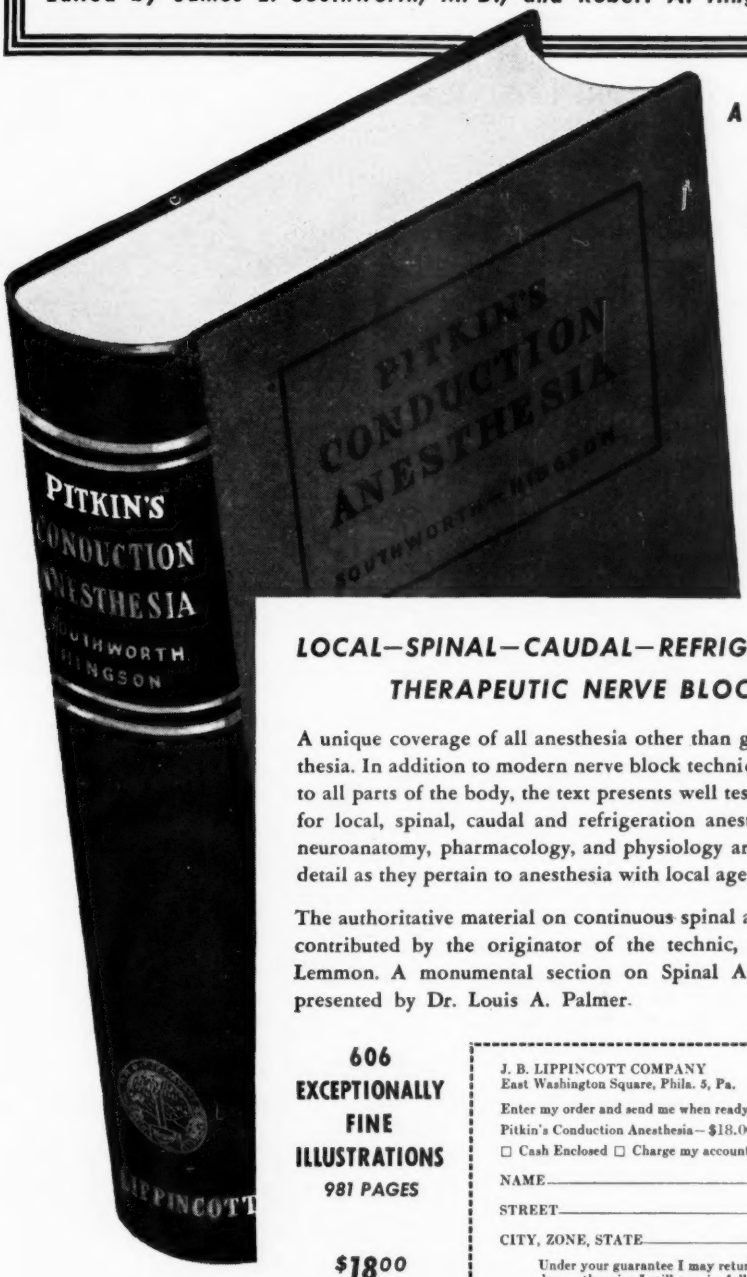

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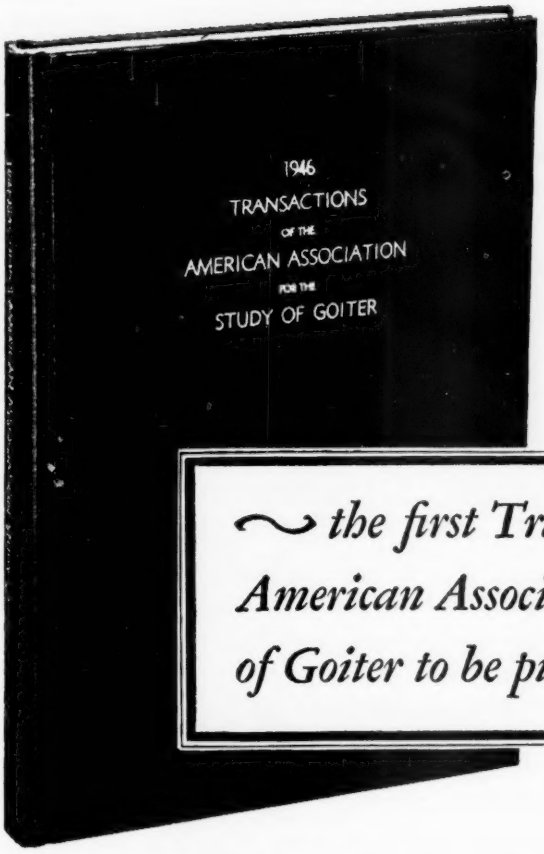

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Published by THE C. V. MOSBY COMPANY, 3207 Washington Blvd., St. Louis 3, U.S.A.

Great Britain Agents: Henry Kimpton, Ltd., 26 Bloomsbury Way, London, W.C.1.
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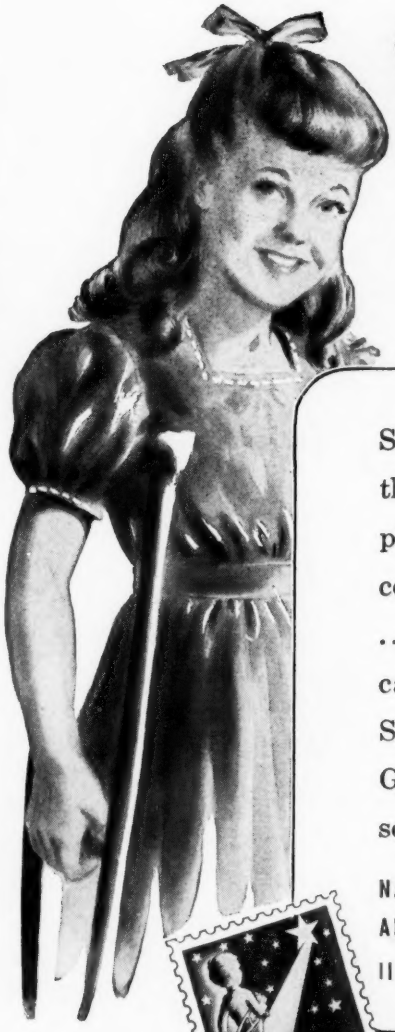

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